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FILE LAST UPDATED: 14 Sep 2003 (20030914/ED)

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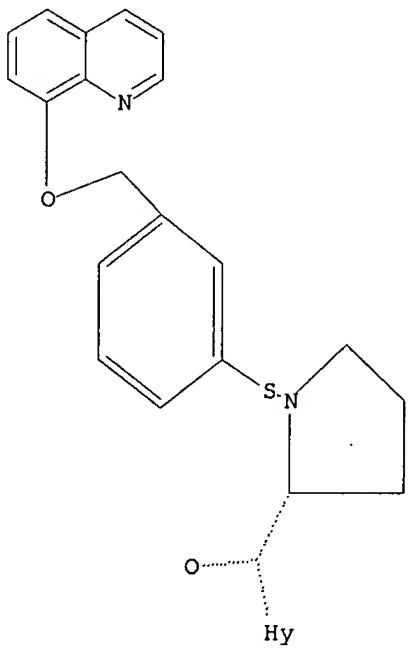
=> d que
L5 STR



Structure attributes must be viewed using STN Express query preparation.
L7 107 SEA FILE=REGISTRY SSS FUL L5
L8 12 SEA FILE=CAPLUS L7

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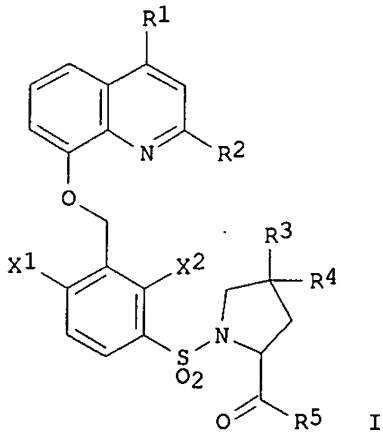
L8 ANSWER 1 OF 12 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2003:470490 CAPLUS

DOCUMENT NUMBER: 139:53305
TITLE: Preparation of N-benzenesulfonyl-L-proline compounds as bradykinin antagonists
INVENTOR(S): Nukii, Seiji; Koike, Hiroki; Kawai, Makoto; Masaru, Yasuhiro
PATENT ASSIGNEE(S): Pfizer Pharmaceutical Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 17 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2003171377	A2	20030620	JP 2001-371081	20011205

PRIORITY APPLN. INFO.: JP 2001-371081 20011205
OTHER SOURCE(S): MARPAT 139:53305
GI



I

AB The title compds. (I) or pharmacol. acceptable salts thereof [X1, X2 = halo, C1-4 alkyl; R1, R2 = H, C1-4 alkyl; R3, R4 = H, halo; R5 = (a) C3-9 diazacycloalkyl optionally substituted C5-11 azabicycloalkyl, (b) C5-11 azabicycloalkyl optionally substituted by C3-9 azacycloalkyl-NH-(C1-4 alkyl), (c) -NH-C1-3 alkyl-CO-C5-11 diazabicycloalkyl, (d) -NH-C1-3 alkyl-CONH-C5-11 azabicycloalkyl where C5-11 azabicycloalkyl is optionally substituted by C1-4 alkyl, (e) C3-9 azacycloalkyl optionally substituted by C3-9 azacycloalkyl, (f) -NH-C1-5 alkyl-NHCO-C4-9 cycloalkyl-NH2] are prepd. These compds. are useful for the treatment of diseases mediated by bradykinin such as inflammation, chronic articular rheumatism, cystitis, brain edema after trauma, hemorrhage, or surgery, brain edema (general), liver cirrhosis, Alzheimer's disease, cardiovascular diseases, pain, cold, allergy, asthma, pancreatitis, burn, viral infection, head trauma, multiple trauma, rhinitis, liver-kidney failure, diabetes, metastasis, neovascularization, corneal opacity, glaucoma, ocular pain, high ocular pressure, amyotrophic lateral sclerosis, Huntington's disease, Parkinson's disease, multiple sclerosis, stroke, cytotoxic brain edema, brain edema related to metabolic disease, osteoarthritis (arthrosis deformans), migraine, neuropathic pain, itching, brain tumor, pseudo-brain tumor,

hydrocephalus, spinal cord injury, spinal cord dropsy, neurodegenerative disease, respiratory disease, diuresis, increase in the excretion of sodium and potassium, chronic obstructive pulmonary disease, brain damage after trauma, and septicemia. Thus, (3S)-3-(1-piperazinyl)-1-azabicyclo[2.2.2]octane was condensed with N-[2,4-dichloro-3-(2,4-dimethylquinolin-8-yloxymethyl)phenylsulfonyl]-L-proline using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride and 1-hydroxybenzotriazole in CH2Cl2 at room temp. overnight to give 8-[[3-[[(2S)-2-[[4-[(3S)-1-azabicyclo[2.2.2]octan-3-yl]-1-piperazinyl]carbonyl]-1-pyrrolidinyl]sulfonyl]-2,6-dichlorobenzyl]oxy]-2,4-dimethylquinoline. The compds. I showed IC50 of 0.1-4 nM for inhibiting the binding of [3H]bradykinin to CHO-K1 cell membrane prepd. from monkey ileum.

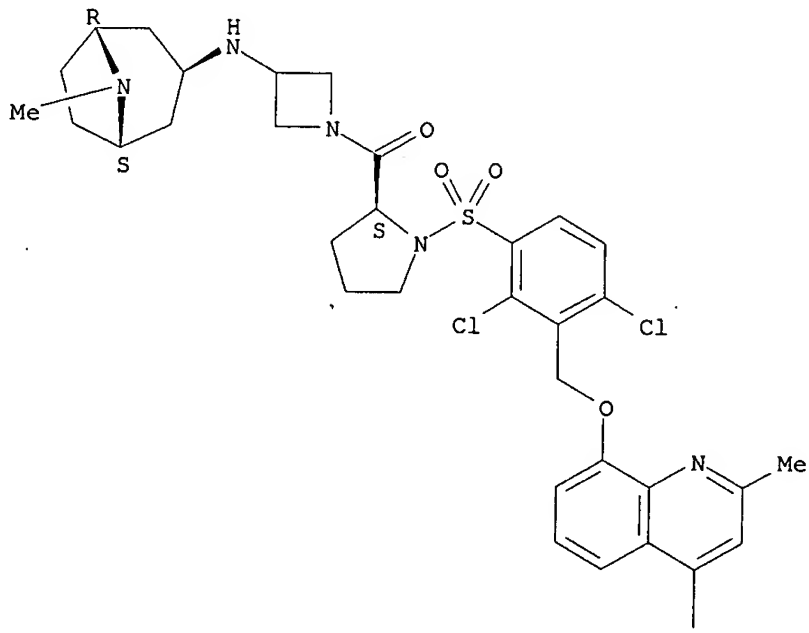
IT **436099-26-2P 436099-43-3P**, 8-[[3-[[(2S)-2-[[4-[(3S)-1-Azabicyclo[2.2.2]octan-3-yl]-1-piperazinyl]carbonyl]-1-pyrrolidinyl]sulfonyl]-2,6-dichlorobenzyl]oxy]-2,4-dimethylquinoline **436099-45-5P**, (2S)-1-[[1-[[2,4-Dichloro-3-[[(2,4-dimethyl-8-quinolyl)oxy]methyl]phenyl]sulfonyl]-2-pyrrolidinyl]carbonyl]-4-piperidinopiperidine **544711-25-3P**, 8-[[3-[[(2S)-2-[[4-[(3S)-1-Azabicyclo[2.2.2]octan-3-yl]-1-piperazinyl]carbonyl]-1-pyrrolidinyl]sulfonyl]-2,6-dichlorobenzyl]oxy]-2,4-dimethylquinoline hydrochloride **544711-26-4P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of N-benzenesulfonyl-L-proline compds. as bradykinin antagonists for treatment of diseases mediated by bradykinin)

RN 436099-26-2 CAPLUS

CN 3-Azetidinamine, 1-[[(2S)-1-[[2,4-dichloro-3-[[(2,4-dimethyl-8-quinolinyl)oxy]methyl]phenyl]sulfonyl]-2-pyrrolidinyl]carbonyl]-N-[(3-exo)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



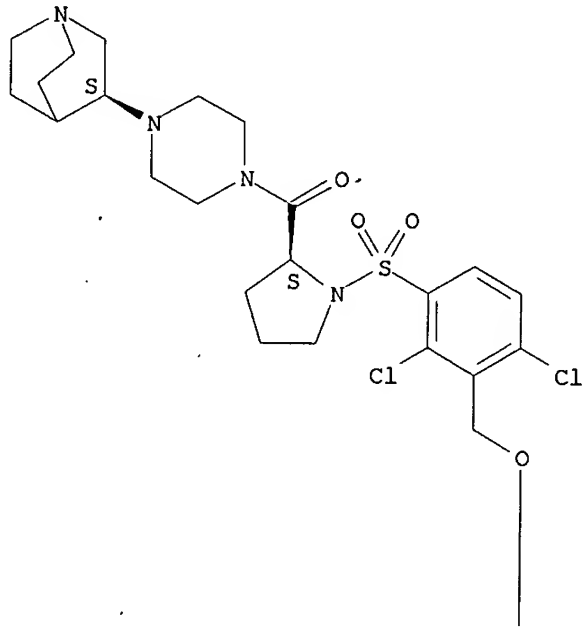
PAGE 2-A

Me

RN 436099-43-3 CAPLUS
CN Piperazine, 1-(3S)-1-azabicyclo[2.2.2]oct-3-yl-4-[[(2S)-1-[[2,4-dichloro-3-[[(2,4-dimethyl-8-quinolinyl)oxy]methyl]phenyl]sulfonyl]-2-pyrrolidinyl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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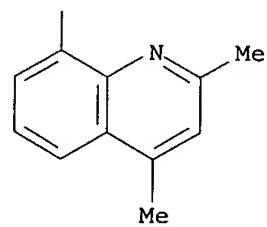
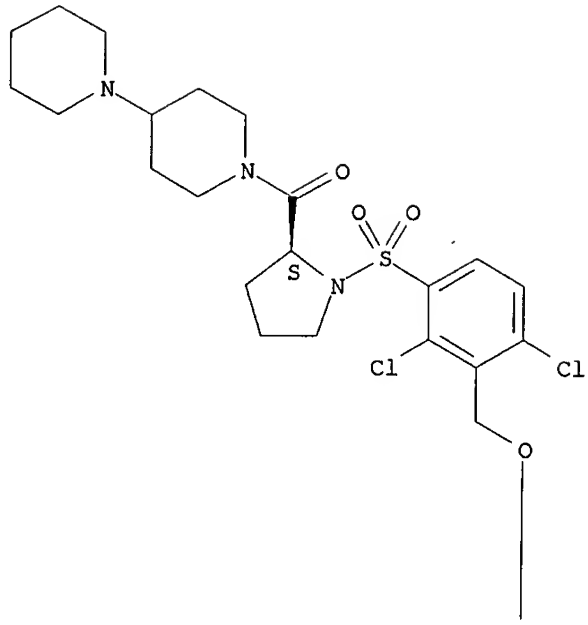


RN 436099-45-5 CAPLUS
CN 1,4'-Bipiperidine, 1'-[[(2S)-1-[[2,4-dichloro-3-[[(2,4-dimethyl-8-quinolinyl)oxy]methyl]phenyl]sulfonyl]-2-pyrrolidinyl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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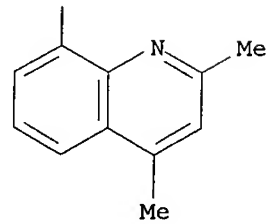
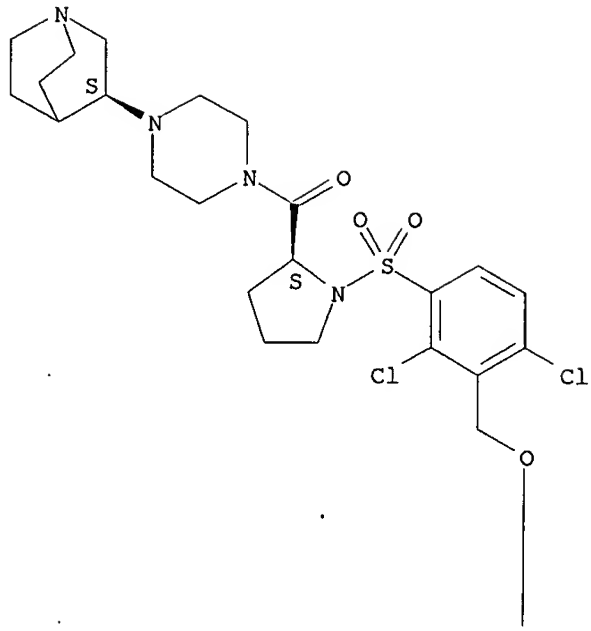


RN 544711-25-3 CAPLUS
CN Piperazine, 1-(3S)-1-azabicyclo[2.2.2]oct-3-yl-4-[[(2S)-1-[[2,4-dichloro-3-[[(2,4-dimethyl-8-quinolinyl)oxy]methyl]phenyl]sulfonyl]-2-pyrrolidinyl]carbonyl]-, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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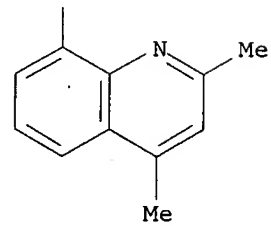
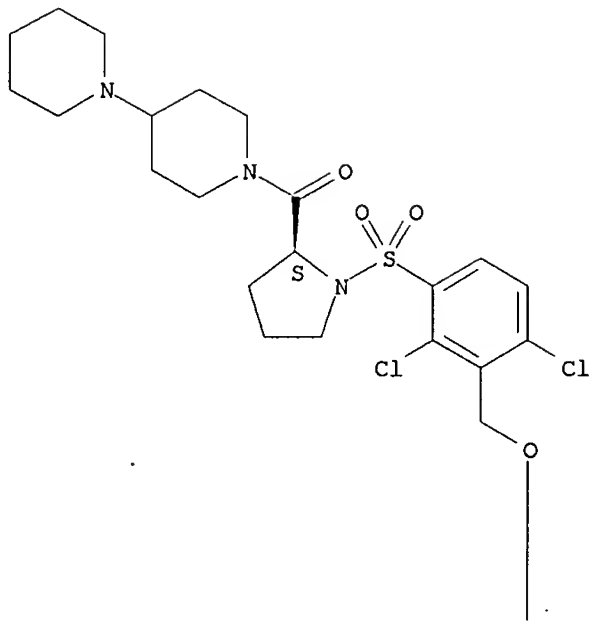


● HCl

RN 544711-26-4 CAPLUS
CN 1,4'-Bipiperidine, 1'-[[(2S)-1-[[2,4-dichloro-3-[[(2,4-dimethyl-8-quinolinyl)oxy]methyl]phenyl]sulfonyl]-2-pyrrolidinyl]carbonyl]-, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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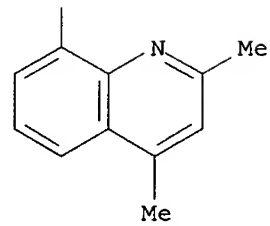

● HCl

L8 ANSWER 2 OF 12 CAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 2002:446120 CAPLUS
DOCUMENT NUMBER: 137:33534
TITLE: Preparation of N-benzenesulfonyl-L-proline compounds as bradykinin antagonists
INVENTOR(S): Katsu, Yasuhiro; Kawai, Makoto; Koike, Hiroki; Nukui, Seiji
PATENT ASSIGNEE(S): Pfizer Inc., USA
SOURCE: Eur. Pat. Appl., 19 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1213289	A1	20020612	EP 2001-310151	20011204
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
BR 2001005775	A	20020813	BR 2001-5775	20011204
JP 2002220387	A2	20020809	JP 2001-371430	20011205
US 2002128271	A1	20020912	US 2001-10863	20011205

PRIORITY APPLN. INFO.: US 2000-251225P P 20001205
OTHER SOURCE(S): MARPAT 137:33534
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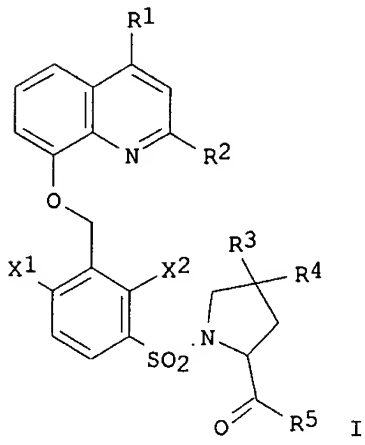


I

AB Proline derivs. I [X1, X2 = halo or C1-4 alkyl; R1, R2 = H or C1-4 alkyl; R3, R4 = H or halo; R5 = C3-9 diazacycloalkyl optionally substituted with C5-11 azabicycloalkyl, C3-9 azacycloalkyl-NH-(C5-11 azabicycloalkyl optionally substituted with C1-4 alkyl), NH-C1-3 alkyl-C(O)-C5-11 diazabicycloalkyl, NH-C1-3 alkyl-C(O)-NH-C5-11 azabicycloalkyl, the C5-11 azabicycloalkyl being optionally substituted with C1-4 alkyl, C3-9 azacycloalkyl optionally substituted with C3-9 azacycloalkyl, or NH-C1-5 alkyl-NHC(O)-C4-9 cycloalkyl-NH] or their pharmaceutically-acceptable salts were prepd. for the treatment of medical conditions mediated by bradykinin, e.g., inflammation, allergic rhinitis, and pain. Thus, 8-[[3-[[(2S)-2-[[4-[(3S)-1-azabicyclo[2.2.2]oct-3-yl]-1-piperazinyl]carbonyl]pyrrolidinyl]sulfonyl]-2,6-dichlorobenzyl]oxy]-2,4-dimethylquinoline hydrochloride was prepd. via acylation of 3(S)-(1-piperazinyl)-1-azabicyclo[2.2.2]octane (prepn. given). The biol. activity of compds. of the invention was detd. by their ability to inhibit the binding of bradykinin at its receptor sites in recombinant human bradykinin B2 receptor expressing CHO-K1 cells (IC50 values for the synthesized compds. were 0.1-4 nM).

IT **436099-25-1P 436099-26-2P 436099-29-5P**
436099-43-3P 436099-45-5P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of N-benzenesulfonyl-L-proline compds. as bradykinin antagonists)

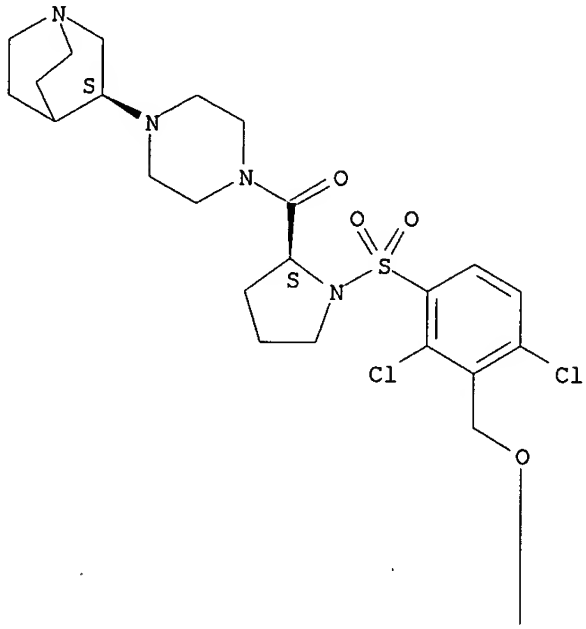
RN 436099-25-1 CAPLUS

CN Piperazine, 1-(3S)-1-azabicyclo[2.2.2]oct-3-yl-4-[[(2S)-1-[[2,4-dichloro-3-

[[(2,4-dimethyl-8-quinolinyl)oxy]methyl]phenyl]sulfonyl]-2-pyrrolidinyl]carbonyl]-, hydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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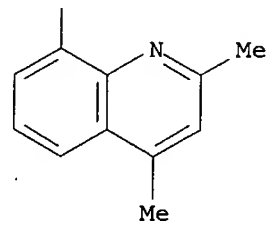
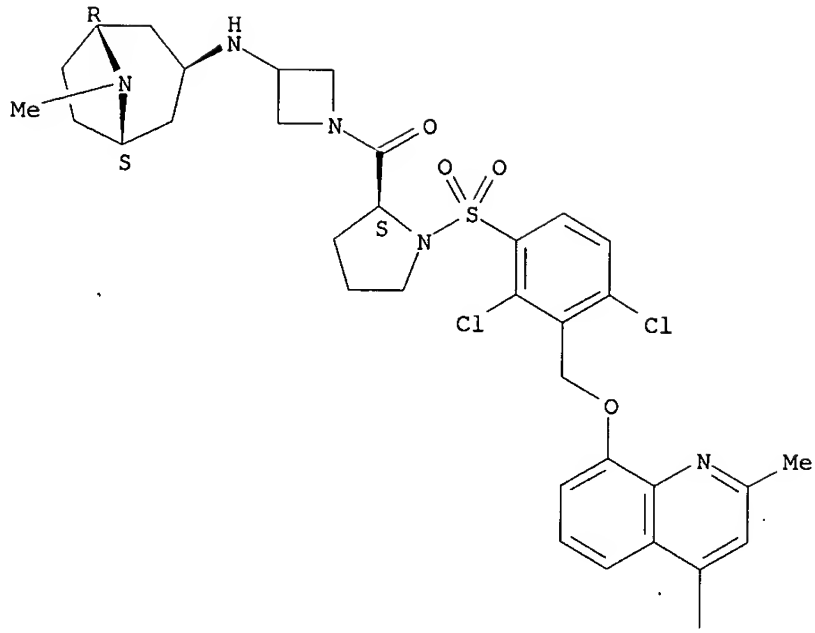


●x HCl

RN 436099-26-2 CAPLUS
CN 3-Azetidinamine, 1-[[(2S)-1-[[2,4-dichloro-3-[[(2,4-dimethyl-8-quinolinyl)oxy]methyl]phenyl]sulfonyl]-2-pyrrolidinyl]carbonyl]-N-[(3-exo)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A

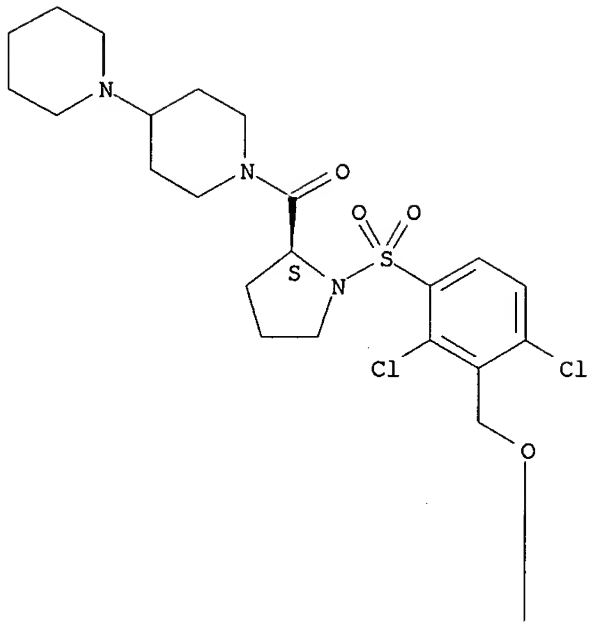


PAGE 2-A

RN 436099-29-5 CAPLUS
CN 1,4'-Bipiperidine, 1'-[[(2S)-1-[[2,4-dichloro-3-[[(2,4-dimethyl-8-quinolinyl)oxy]methyl]phenyl]sulfonyl]-2-pyrrolidinyl]carbonyl]-, hydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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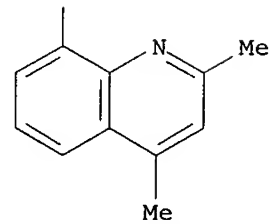
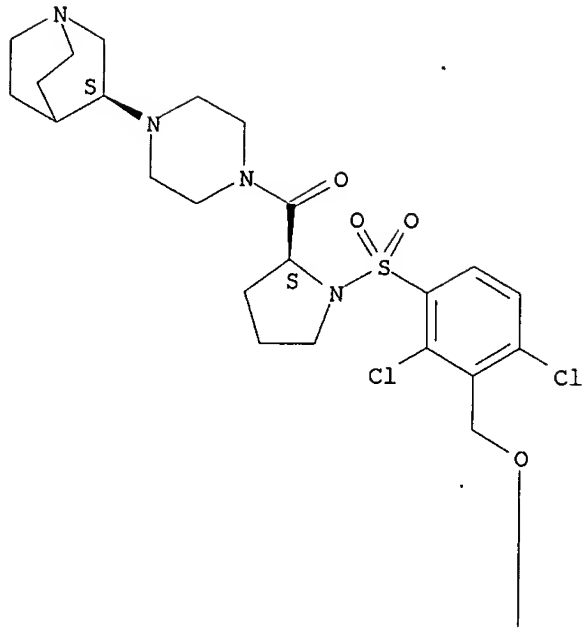


●x HCl

RN 436099-43-3 CAPLUS
CN Piperazine, 1-(3S)-1-azabicyclo[2.2.2]oct-3-yl-4-[[(2S)-1-[[2,4-dichloro-3-[[(2,4-dimethyl-8-quinolinyl)oxy]methyl]phenyl]sulfonyl]-2-pyrrolidinyl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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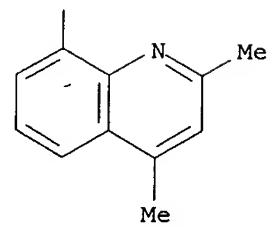
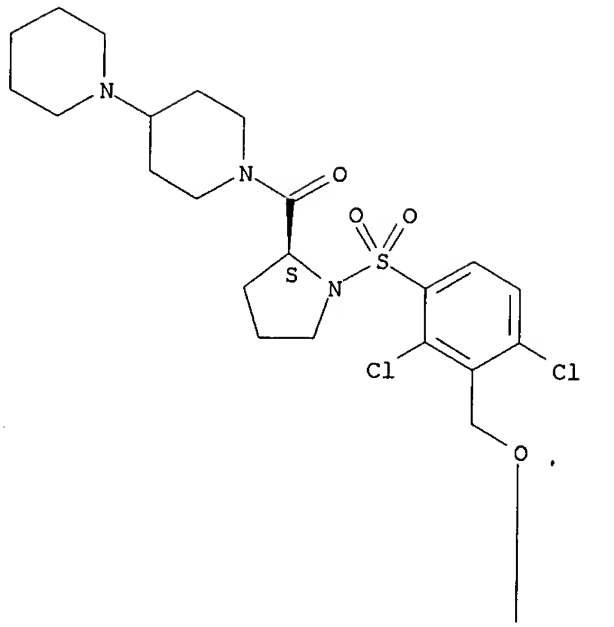


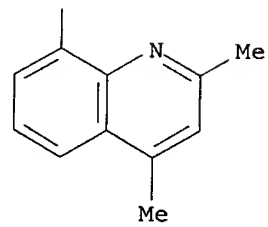
RN 436099-45-5 CAPLUS
CN 1,4'-Bipiperidine, 1'-[[(2S)-1-[[2,4-dichloro-3-[[(2,4-dimethyl-8-quinolinyl)oxy]methyl]phenyl]sulfonyl]-2-pyrrolidinyl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 2-A



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 3 OF 12 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2002:355710 CAPLUS
DOCUMENT NUMBER: 137:304928
TITLE: Preliminary mutational analysis of the human kinin B2 receptor for nonpeptide antagonist ligands recognition
AUTHOR(S): Meini, Stefania; Cucchi, Paola; Zappitelli, Sabrina; Rotondaro, Luigi; Quartara, Laura; Giolitti, Alessandro; Maggi, Carlo Alberto
CORPORATE SOURCE: Department of Pharmacology, Menarini Ricerche, Florence, Italy
SOURCE: Canadian Journal of Physiology and Pharmacology (2002), 80(4), 303-309
CODEN: CJPPA3; ISSN: 0008-4212
PUBLISHER: National Research Council of Canada
DOCUMENT TYPE: Journal
LANGUAGE: English
AB FR173657, LF16,0335, and LF16,0687 are nonpeptide antagonists, endowed

with high affinity and selectivity for the human kinin B2 receptor. The kinin B2 receptor belongs to the family of G-protein-coupled receptors with seven transmembrane (TM) helixes. In the present study, the authors aimed, through computer-assisted modeling and mutagenesis, to identify residues in the human B2 receptor (hB2R) amino acid sequence that are involved in nonpeptide antagonist binding to build up exptl. data as a first step towards a mol. model of nonpeptide ligands binding site. Fourteen amino acid residues within the TM segments were mutated to alanine. The wild type and mutant receptors were stably expressed in Chinese hamster ovary (dhfr-) cells and tested for their ability to bind agonist ([3H]bradykinin) and peptide antagonist ([3H]MEN11270) radioligands. The affinity of nonpeptide ligands was detd. by heterologous competition expts. using the above radioligands. The authors found that some mutations in TM2 (W86A) and TM7 (Y295A, N297A) impair the binding affinity of the three nonpeptide antagonists. Some mutated residues in TM3 (S117A) and TM6 (W256A) reduce the affinity of LF16,0335 and LF16,0687 only. Results are discussed to build up a hypothesis for the likely different interactions of various nonpeptide ligands with the B2 receptor.

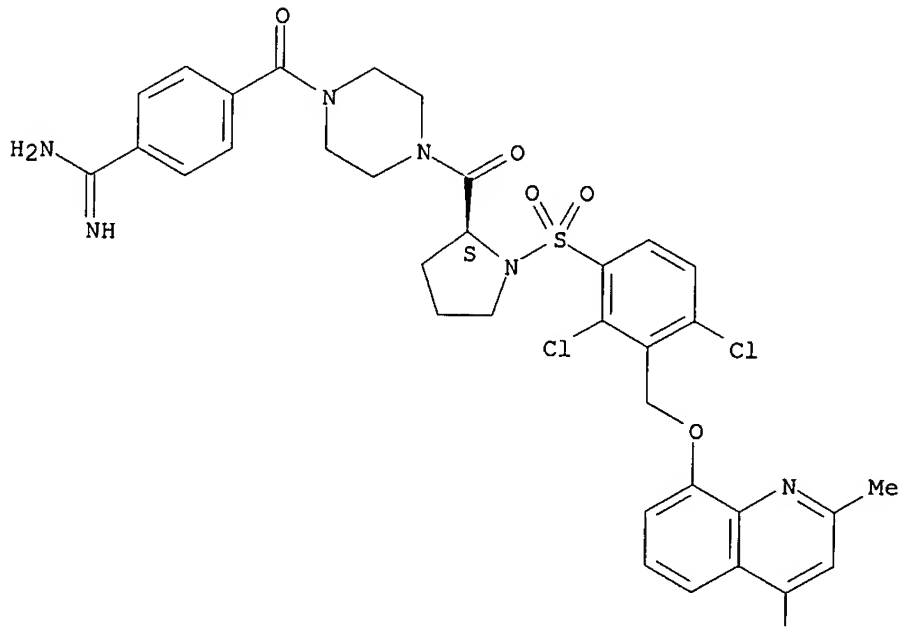
IT **202602-34-4**, LF16,0335
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(preliminary mutational anal. of human kinin B2 receptor for nonpeptide antagonist ligands recognition)

RN 202602-34-4 CAPLUS

CN Piperazine, 1-[4-(aminoiminomethyl)benzoyl]-4-[[(2S)-1-[[2,4-dichloro-3-[[(2,4-dimethyl-8-quinolinyl)oxy]methyl]phenyl]sulfonyl]-2-pyrrolidinyl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

PAGE 1-A



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REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 4 OF 12 CAPLUS COPYRIGHT 2003 ACS on STN ✓

ACCESSION NUMBER: 2002:126841 CAPLUS
DOCUMENT NUMBER: 136:273537
TITLE: Pharmacological and functional characterization of the guinea-pig B2 bradykinin receptor stably expressed in CHO-K1 cell line
AUTHOR(S): Robert, C.; Pruneau, D.; Paquet, J.-L.
CORPORATE SOURCE: Groupe de Pharmacologie des Recepteurs, Centre de Recherche, Laboratoires Fournier, Dijon, 21121, Fr.
SOURCE: British Journal of Pharmacology (2002), 135(2), 462-468
CODEN: BJPCBM; ISSN: 0007-1188
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English

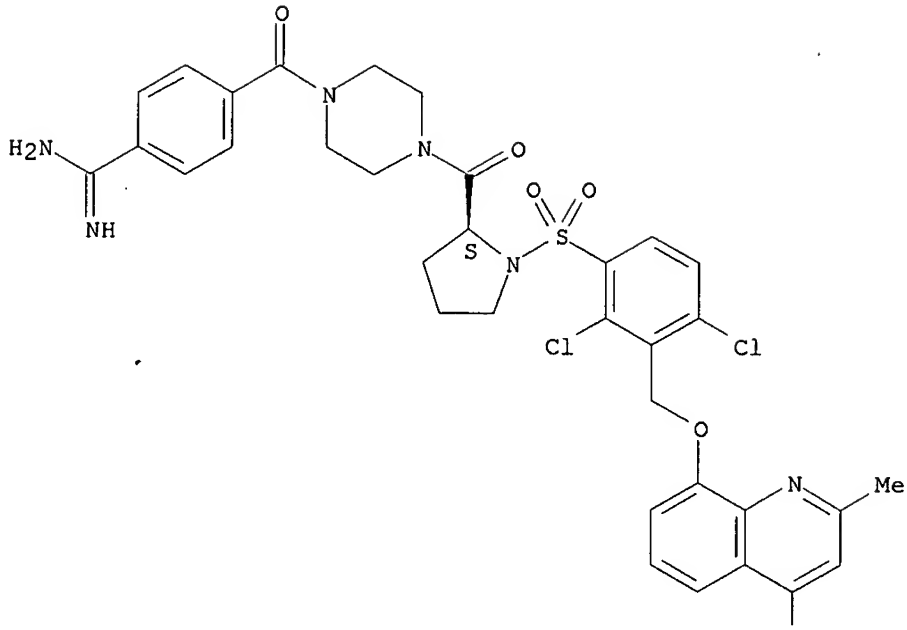
AB 1 In the present study, pharmacol. properties of a bradykinin B2 receptor amplified either from guinea-pig ileum or lung and homologous to the previously reported sequence except two amino-acid changes L124.fwdarw.P and N227.fwdarw.Y in the receptor protein were characterized. 2 Tritiated bradykinin ([3H]-BK) specifically bound to the cloned guinea-pig B2 bradykinin receptor stably expressed in Chinese hamster ovary cells (CHO-K1) with a KD value of 0.29.+-.0.07 nM. In competition expts., bradykinin (BK) affinity const. value was 0.21.+-.0.05 nM while the two specific kinin B1 ligands, des-Arg9-bradykinin (DBK) and des-Arg9-Leu8-bradykinin (DLBK) were unable to compete with [3H]-BK. As the specific peptide antagonist D-Arg-[Hyp3,Thi5,D-Tic7,Oic8]-bradykinin (HOE140), (E)-3-(6-acetamido-3-pyridil)-N-[-N-[2,4-dichloro-3-[(2-methyl-8-quinolinyl)oxymethyl]phenyl]-N-methylaminocarbonylmethyl]acrylamide (FR173657) and 1-[[[3-(2,4-dimethylquinolin-8-yl)oxymethyl]-2,4-dichlorophenyl]sulfonyl]-2(S)-[[4-[4-(aminoiminomethyl)-phenylcarbonyl]piperazin-1-yl]carbonyl]pyrrolidine (LF16-0335C) exhibited a high affinity for this receptor with Ki values of 7.34.+-.2.45 nM and 8.54.+-.1.55 nM resp. 3 BK and kallidin (KD) increased inositol phosphates (IPs) levels with EC50 values of 0.44.+-.0.12 nM and 6.88.+-.0.28 nM, resp. Neither DLBK nor DBK (0.01 nM to 10 .mu.M) stimulated or inhibited IPs turnover and as expected HOE140 did not raise IPs prodn. HOE140 (0.1 .mu.M) and LF 16-0335c (1 .mu.M) right shifted the BK response curve with pKB values of 9.2.+-.0.4 and 8.4.+-.0.3, resp. 4 The results indicate that this cloned guinea-pig receptor displayed typical pharmacol. properties of a bradykinin B2 receptor and support the existence of a single B2 receptor in this species.

IT **202720-59-0**, LF16-0335C
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(pharmacol. and functional characterization of guinea-pig B2 bradykinin receptor stably expressed in CHO-K1 cell line)

RN 202720-59-0 CAPLUS
CN Piperazine, 1-[4-(aminoiminomethyl)benzoyl]-4-[[(2S)-1-[[2,4-dichloro-3-[[(2,4-dimethyl-8-quinolinyl)oxy]methyl]phenyl]sulfonyl]-2-pyrrolidinyl]carbonyl]-, dihydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

PAGE 1-A



PAGE 2-A

● 2 HCl

REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 5 OF 12 CAPLUS COPYRIGHT 2003 ACS on STN ✓

ACCESSION NUMBER: 2001:864032 CAPLUS
DOCUMENT NUMBER: 136:96201
TITLE: Palmitoylation of the Human Bradykinin B2 Receptor Influences Ligand Efficacy
AUTHOR(S): Pizard, Anne; Blaukat, Andree; Michineau, Stephanie; Dikic, Ivan; Mueller-Esterl, Werner; Alhenc-Gelas, Francois; Rajerison, Rabary M.
CORPORATE SOURCE: INSERM Unite 367, Paris, 75005, Fr.
SOURCE: Biochemistry (2001), 40(51), 15743-15751
CODEN: BICHAW; ISSN: 0006-2960
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB To investigate the palmitoylation of the human bradykinin B2 receptor, we have mutated individually or simultaneously into glycine two potential acylation sites (cysteines 324 and 329) located in the carboxyl terminus of the receptor and evaluated the effects of these mutations by transfection in COS-7, CHO-K1, and HEK 293T. The wild-type receptor and the single mutants, but not the double mutant, incorporated [3H]palmitate,

indicating that the receptor carboxyl tail can be palmitoylated at both sites. The mutants did not differ from the wild-type receptor for the kinetics of [3H]bradykinin binding, the basal and bradykinin-stimulated coupling to phospholipases C and A2, and agonist-induced phosphorylation. The nonpalmitoylated receptor had a 30% reduced capacity to internalize [3H]bradykinin. This indicates that palmitoylation does not influence the basal activity of the receptor and its agonist-driven activation. However, the mutants triggered phospholipid metab. and MAP kinase activation in response to B2 receptor antagonists. Pseudopeptide and nonpeptide compds. that behaved as antagonists on the wild-type receptor became agonists on the nonpalmitoylated receptor and produced phospholipases C and A2 responses of 25-50% as compared to that of bradykinin. These results suggest that palmitoylation is required for the stabilization of the receptor-ligand complex in an uncoupled conformation.

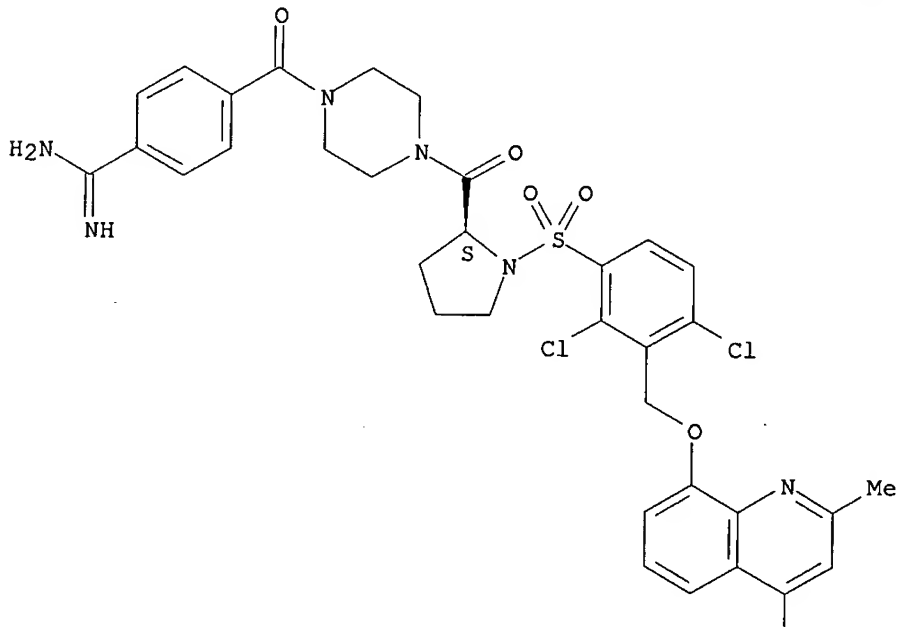
IT **202602-34-4**, LF 160335
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(palmitoylation of the human bradykinin B2 receptor influences ligand efficacy)

RN 202602-34-4 CAPLUS

CN Piperazine, 1-[4-(aminoiminomethyl)benzoyl]-4-[[(2S)-1-[[2,4-dichloro-3-[[(2,4-dimethyl-8-quinolinyl)oxy]methyl]phenyl]sulfonyl]-2-pyrrolidinyl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

PAGE 1-A



PAGE 2-A

REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 6 OF 12 CAPLUS COPYRIGHT 2003 ACS on STN ✓

ACCESSION NUMBER: 2001:846328 CAPLUS
DOCUMENT NUMBER: 136:96200
TITLE: Control of conformational equilibria in the human B2 bradykinin receptor: Modeling of nonpeptidic ligand action and comparison to the rhodopsin structure
AUTHOR(S): Marie, Jacky; Richard, Eric; Pruneau, Didier; Paquet, Jean-Luc; Siatka, Christian; Larguier, Renee; Ponce, Cecilia; Vassault, Philippe; Groblewski, Thierry; Maigret, Bernard; Bonnafous, Jean-Claude
CORPORATE SOURCE: INSERM U439, Montpellier, 34090, Fr.
SOURCE: Journal of Biological Chemistry (2001), 276(44), 41100-41111
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A prototypic study of the mol. mechanisms of activation or inactivation of peptide hormone G protein-coupled receptors was carried out on the human B2 bradykinin receptor. A detailed pharmacol. anal. of receptor mutants possessing either increased constitutive activity or impaired activation or ligand recognition allowed the authors to propose key residues participating in intramol. interaction networks stabilizing receptor inactive or active conformations: Asn113 and Tyr115 (TM III), Trp256 and Phe259 (TM VI), Tyr295 (TM VII) which are homologous of the rhodopsin residues Gly120, Glu122, Trp265, Tyr268, and Lys296, resp. An essential exptl. was the spatial proximity between Asn113, which is the cornerstone of inactive conformations, and Trp256 which plays a subtle role in controlling the balance between active and inactive conformations. Mol. modeling and mutagenesis data showed that Trp256 and Tyr295 constitute, together with Gln288, receptor contact points with original nonpeptidic ligands. It provided an explanation for the ligand inverse agonist behavior on the WT receptor, with underlying restricted motions of TMs III, VI, and VII, and its agonist behavior on the Ala113 and Phe256 constitutively activated mutants. These data on the B2 receptor emphasize that conformational equil. are controlled in a coordinated fashion by key residues which are located at strategic positions for several G protein-coupled receptors. They are discussed in comparison with the recently detd. rhodopsin crystallog. structure.

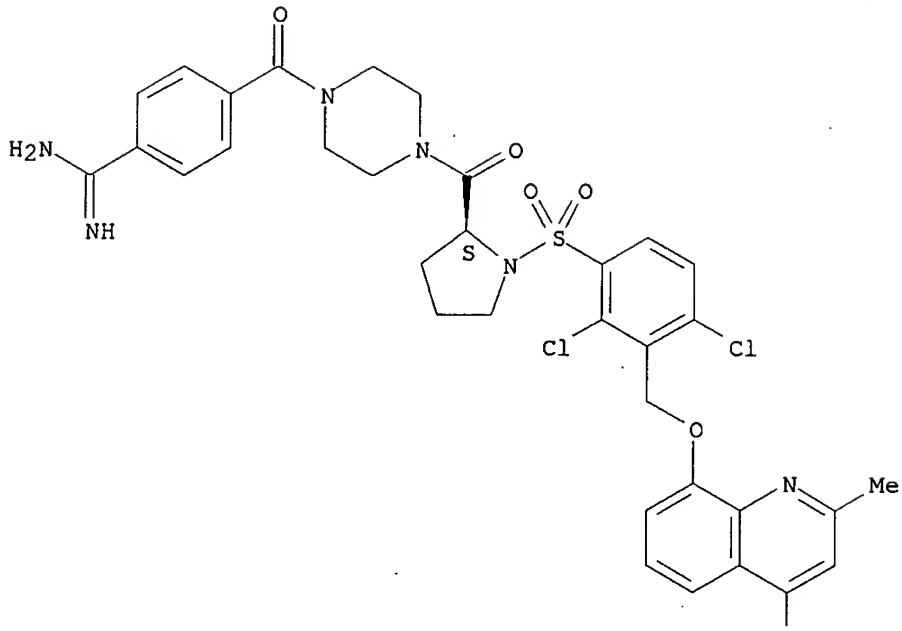
IT **202602-34-4**, LF 16-0335 **388569-99-1**, LH 18-1300
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(human B2 bradykinin receptor conformational equilibia control and modeling of nonpeptidic ligand action and comparison to rhodopsin structure)

RN 202602-34-4 CAPLUS

CN Piperazine, 1-[4-(aminoiminomethyl)benzoyl]-4-[[(2S)-1-[[2,4-dichloro-3-[[(2,4-dimethyl-8-quinolinyl)oxy]methyl]phenyl]sulfonyl]-2-pyrrolidinyl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

PAGE 1-A

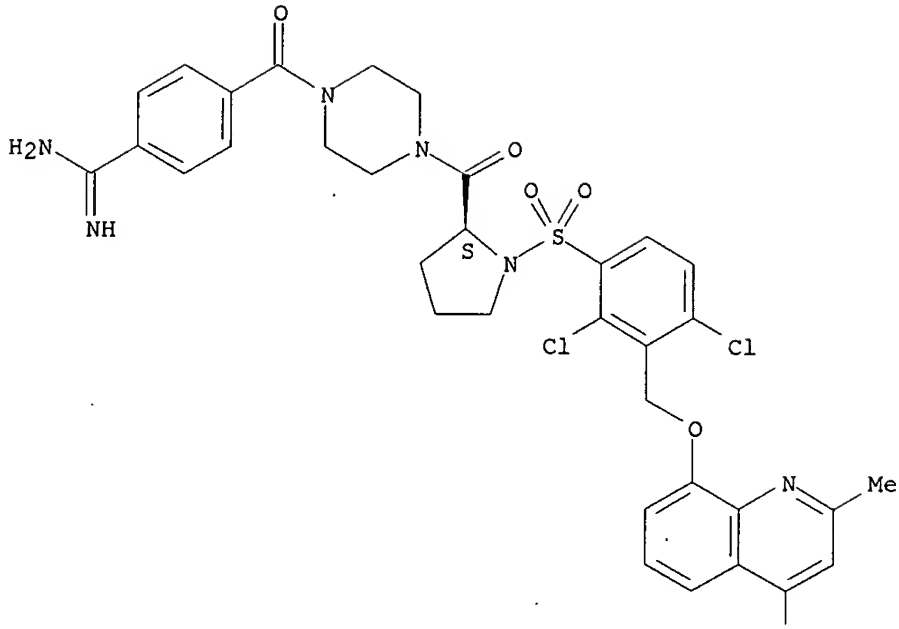


PAGE 2-A

RN 388569-99-1 CAPLUS
CN Piperazine, 1-[4-(aminoiminomethyl)benzoyl]-4-[[(2S)-1-[[2,4-dichloro-3-[[[4-(1H-imidazol-1-yl)-2-methyl-8-quinolinyl]oxy]methyl]phenyl]sulfonyl]-2-pyrrolidinyl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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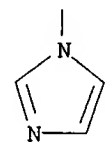

REFERENCE COUNT: 70 THERE ARE 70 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 7 OF 12 CAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 2000:608743 CAPLUS
DOCUMENT NUMBER: 133:207823
TITLE: Heterocyclic benzenesulfonamide compounds useful as bradykinin antagonists and their preparation and use
INVENTOR(S): Dodey, Pierre; Barth, Martine; Bondoux, Michel
PATENT ASSIGNEE(S): Fournier Industrie Et Sante, Fr.
SOURCE: PCT Int. Appl., 118 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000050418	A1	20000831	WO 2000-FR396	20000217

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA,

MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
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BR 2000008221	A	20011120	BR 2000-8221	20000217
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EE 200100444	A	20021216	EE 2001-444	20000217
AT 245640	E	20030815	AT 2000-906414	20000217
US 6479515	B1	20021112	US 2001-889965	20010724
ZA 2001006250	A	20020730	ZA 2001-6250	20010730
NO 2001004048	A	20010820	NO 2001-4048	20010820
BG 105840	A	20020430	BG 2001-105840	20010824
HR 2001000619	A1	20020831	HR 2001-619	20010824

PRIORITY APPLN. INFO.: FR 1999-2412 A 19990226
WO 2000-FR396 W 20000217

OTHER SOURCE(S): MARPAT 133:207823
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The invention concerns title compds. I [Het1 = 5-membered N heterocycle, particularly imidazole, pyrazole, or triazole, bound at N; Het2 = 4- to 6-membered N heterocycle selected from morpholine and certain (un)substituted azetidines, pyrrolines, pyrrolidines, piperidines, and thiazolidines, all bound at N] and their addn. salts. The invention also concerns a method for prepg. I, and the use of I in therapy, particularly for treating bradykinin-related pathologies. Uses of I for treating pain, inflammation, and severe traumatic shock are specifically claimed. Over 200 examples were prepd. For instance, 8-hydroxy-4-(1H-imidazol-1-yl)-2-methylquinoline was etherified with N-[[3-(bromomethyl)-2,4-dichlorophenyl]sulfonyl]-L-proline Me ester using NaH in DMF (68%), followed by sapon. of the Me ester (89%), amidation with N-(3-aminopropyl)-4-cyanobenzamide trifluoroacetate (81%), conversion of the cyano group to amidino in 3 steps (98%, 95%, 66%), and salification in MeOH (75%), to give title compd. II as the bismethanesulfonate. (III). In a test for inhibition of [3H]-bradykinin binding to B2 receptors expressed in CHO cells, III had a Ki of 0.24 nM. III also inhibited bradykinin-induced contraction of isolated human umbilical vein, with a pA2 of 10.

IT **290343-49-6P**, 8-[[2,6-Dichloro-3-[[2-(S)-[[4-(4-pyridinyl)-1-piperazinyl]carbonyl]-1-pyrrolidinyl]sulfonyl]phenyl]methoxy]-4-(1H-imidazol-1-yl)-2-methylquinoline **290343-51-0P**, 8-[[2,6-Dichloro-3-[[2-(S)-[[4-(2-pyridinyl)-1-piperazinyl]carbonyl]-1-pyrrolidinyl]sulfonyl]phenyl]methoxy]-4-(1H-imidazol-1-yl)-2-methylquinoline **290344-02-4P**, 8-[[2,6-Dichloro-3-[[2-(S)-[[4-(2-pyridinyl)-1-piperazinyl]carbonyl]-1-pyrrolidinyl]sulfonyl]phenyl]methoxy]-2-methyl-4-(1H-1,2,4-triazol-1-yl)quinoline **290344-04-6P**, 8-[[2,6-Dichloro-3-[[2-(S)-(4-morpholinylcarbonyl)-1-pyrrolidinyl]sulfonyl]phenyl]methoxy]-4-(1H-imidazol-1-yl)-2-

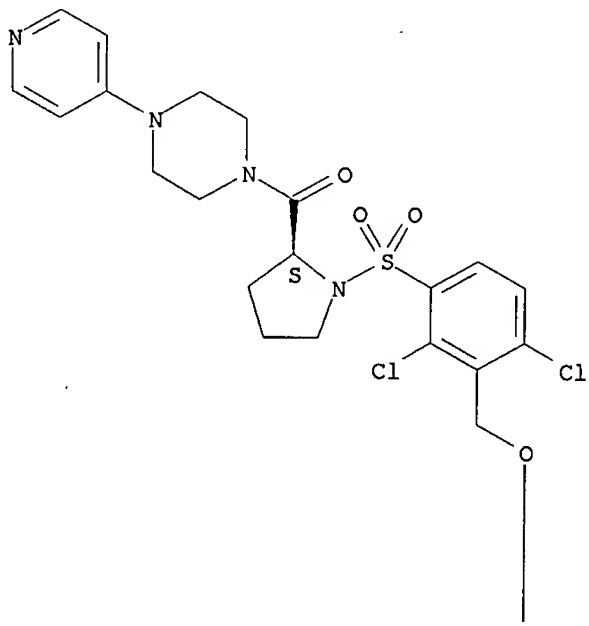
methylquinoline **290344-06-8P**, 8-[[2,6-Dichloro-3-[[2-(S)-[(4-methyl-1-piperazinyl)carbonyl]-1-pyrrolidinyl]sulfonyl]phenyl]methoxy]-4-(1H-imidazol-1-yl)-2-methylquinoline **290344-08-0P**, 8-[[2,6-Dichloro-3-[[2-(S)-[(4-phenyl-1-piperazinyl)carbonyl]-1-pyrrolidinyl]sulfonyl]phenyl]methoxy]-4-(1H-imidazol-1-yl)-2-methylquinoline **290344-19-3P**, 8-[[2,6-Dichloro-3-[[2-(S)-(1-piperazinylcarbonyl)-1-pyrrolidinyl]sulfonyl]phenyl]methoxy]-4-(1H-imidazol-1-yl)-2-methylquinoline bistrifluoroacetate **290344-20-6P**, 8-[[2,6-Dichloro-3-[[2-(S)-[[4-(2-pyridinylmethyl)-1-piperazinyl]carbonyl]-1-pyrrolidinyl]sulfonyl]phenyl]methoxy]-4-(1H-imidazol-1-yl)-2-methylquinoline **290344-22-8P**, 8-[[2,6-Dichloro-3-[[2-(S)-[[4-(3-pyridinylmethyl)piperazinyl]carbonyl]-1-pyrrolidinyl]sulfonyl]phenyl]methoxy]-4-(1H-imidazol-1-yl)-2-methylquinoline **290344-24-0P**, 8-[[2,6-Dichloro-3-[[2-(S)-[[4-(4-pyridinylmethyl)-1-piperazinyl]carbonyl]-1-pyrrolidinyl]sulfonyl]phenyl]methoxy]-4-(1H-imidazol-1-yl)-2-methylquinoline
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(drug candidate; prepn. of heterocyclic benzenesulfonamide derivs. as bradykinin antagonists)

RN 290343-49-6 CAPLUS

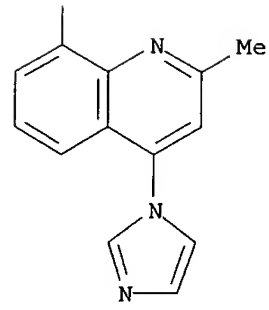
CN Piperazine, 1-[[(2S)-1-[[2,4-dichloro-3-[[[4-(1H-imidazol-1-yl)-2-methyl-8-quinolinyl]oxy]methyl]phenyl]sulfonyl]-2-pyrrolidinyl]carbonyl]-4-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



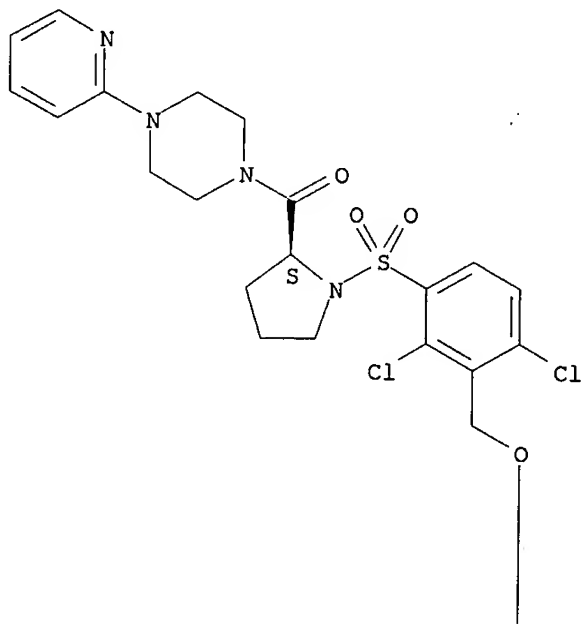
PAGE 2-A



RN 290343-51-0 CAPLUS
CN Piperazine, 1-[[(2S)-1-[[2,4-dichloro-3-[[[4-(1H-imidazol-1-yl)-2-methyl-8-quinolinyl]oxy]methyl]phenyl]sulfonyl]-2-pyrrolidinyl]carbonyl]-4-(2-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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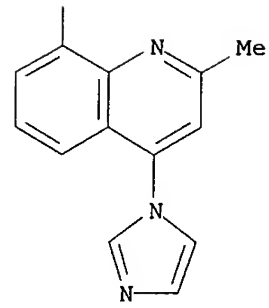
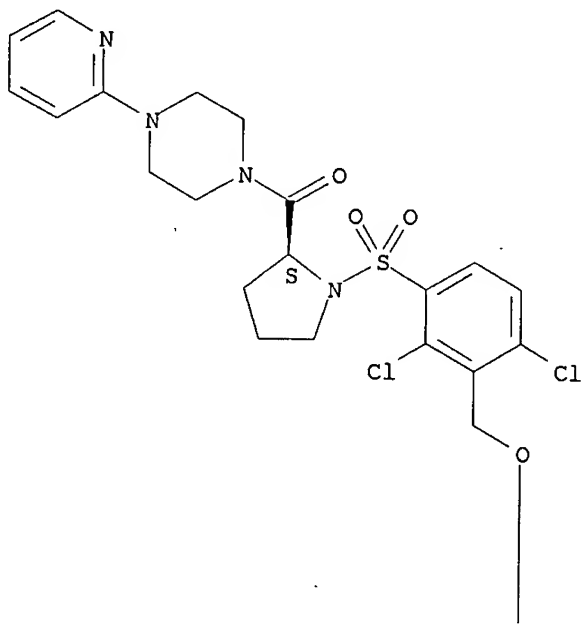


RN 290344-02-4 CAPLUS
CN Piperazine, 1-[[(2S)-1-[[2,4-dichloro-3-[[[2-methyl-4-(1H-1,2,4-triazol-1-yl)-8-quinolinyl]oxy]methyl]phenyl]sulfonyl]-2-pyrrolidinyl]carbonyl]-4-(2-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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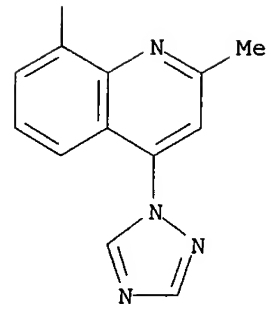
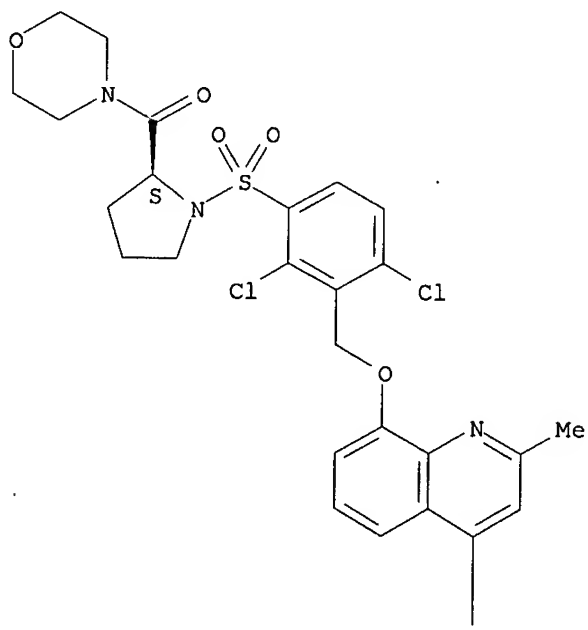


RN 290344-04-6 CAPLUS
CN Morpholine, 4-[[(2S)-1-[[2,4-dichloro-3-[[[4-(1H-imidazol-1-yl)-2-methyl-8-quinolinyl]oxy]methyl]phenyl]sulfonyl]-2-pyrrolidinyl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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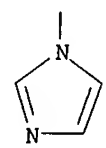
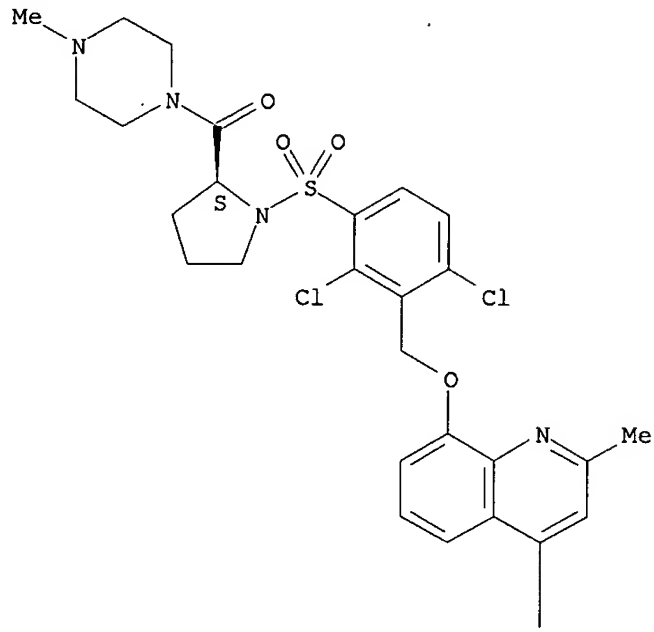


RN 290344-06-8 CAPLUS
CN Piperazine, 1-[[(2S)-1-[[2,4-dichloro-3-[[[4-(1H-imidazol-1-yl)-2-methyl-8-

quinolinyl]oxy]methyl]phenyl]sulfonyl]-2-pyrrolidinyl]carbonyl]-4-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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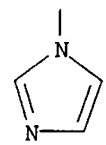
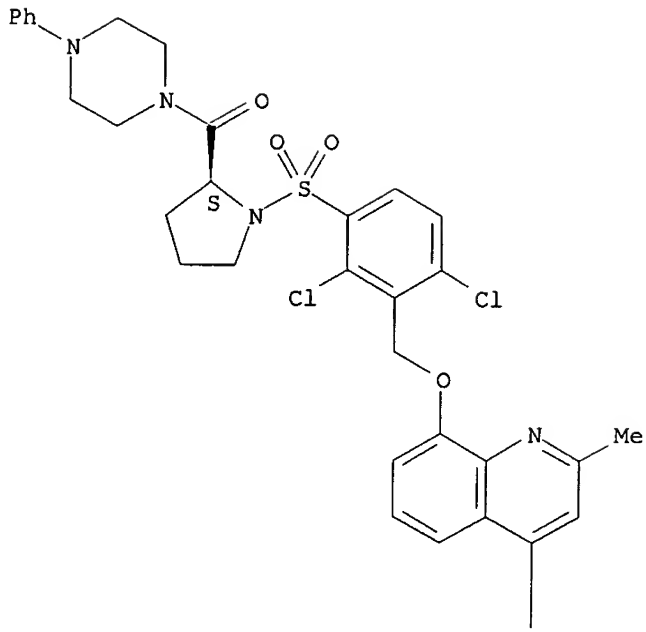


RN 290344-08-0 CAPLUS

CN Piperazine, 1-[[(2S)-1-[[2,4-dichloro-3-[[[4-(1H-imidazol-1-yl)-2-methyl-8-quinolinyl]oxy]methyl]phenyl]sulfonyl]-2-pyrrolidinyl]carbonyl]-4-phenyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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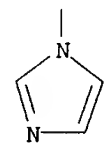


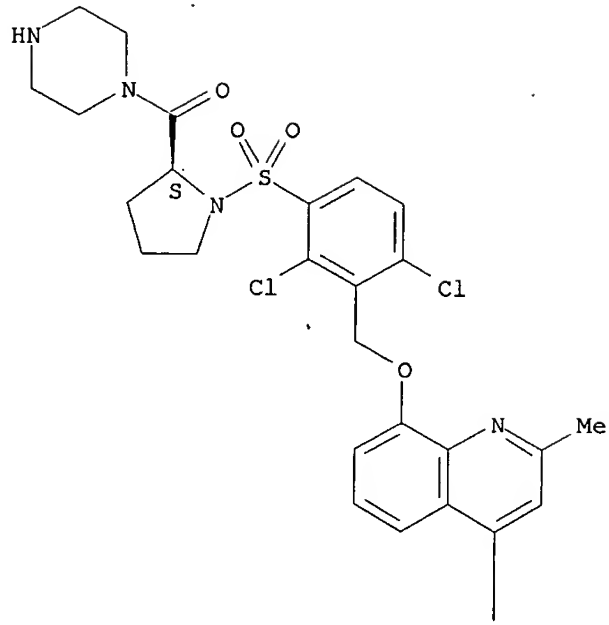
RN 290344-19-3 CAPLUS
CN Piperazine, 1-[[(2S)-1-[[2,4-dichloro-3-[[[4-(1H-imidazol-1-yl)-2-methyl-8-quinolinyl]oxy]methyl]phenyl]sulfonyl]-2-pyrrolidinyl]carbonyl]-, bis(trifluoroacetate) (9CI) (CA INDEX NAME)

CM 1

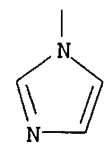
CRN 290344-18-2
CMF C29 H30 Cl2 N6 O4 S

Absolute stereochemistry.

PAGE 1-A

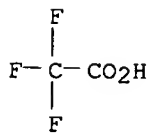


PAGE 2-A



CM 2

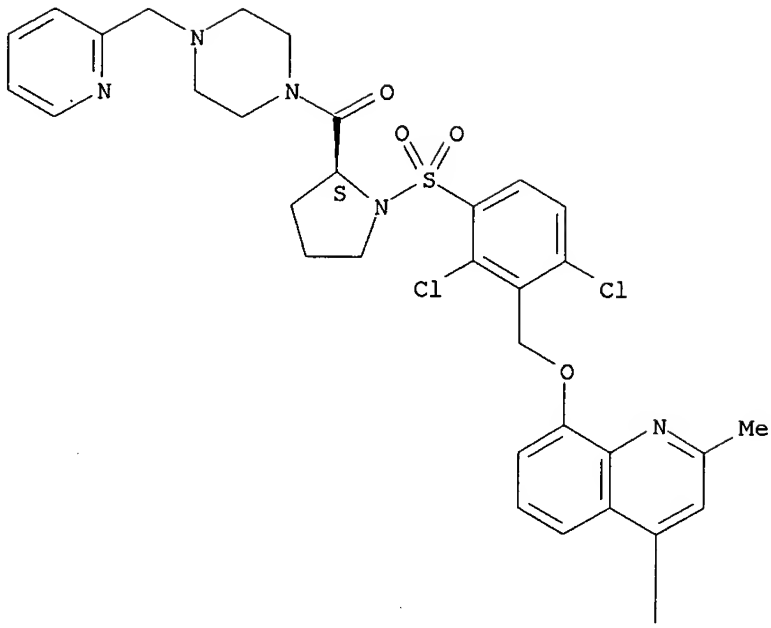
CRN 76-05-1
CMF C2 H F3 O2



RN 290344-20-6 CAPLUS
CN Piperazine, 1-[[(2S)-1-[[2,4-dichloro-3-[[[4-(1H-imidazol-1-yl)-2-methyl-8-quinolinyl]oxy]methyl]phenyl]sulfonyl]-2-pyrrolidinyl]carbonyl]-4-(2-pyridinylmethyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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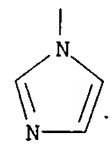
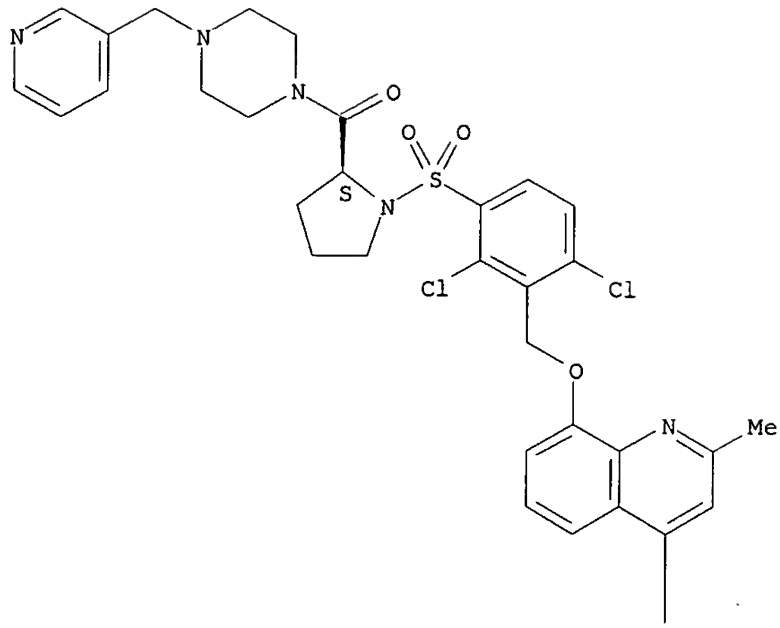


RN 290344-22-8 CAPLUS
CN Piperazine, 1-[[(2S)-1-[[2,4-dichloro-3-[[[4-(1H-imidazol-1-yl)-2-methyl-8-quinolinyl]oxy]methyl]phenyl]sulfonyl]-2-pyrrolidinyl]carbonyl]-4-(3-pyridinylmethyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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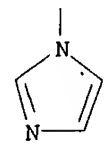
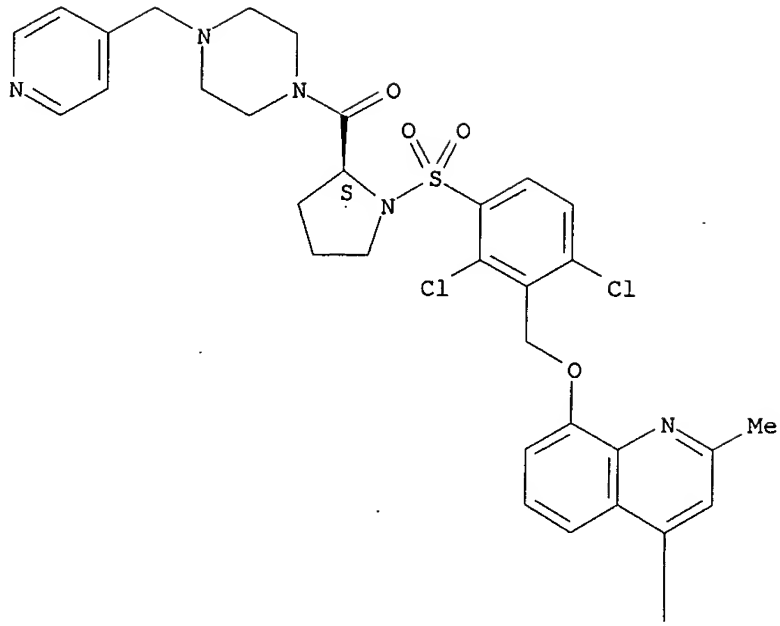


RN 290344-24-0 CAPLUS
CN Piperazine, 1-[[(2S)-1-[[2,4-dichloro-3-[[[4-(1H-imidazol-1-yl)-2-methyl-8-quinolinyl]oxy]methyl]phenyl]sulfonyl]-2-pyrrolidinyl]carbonyl]-4-(4-pyridinylmethyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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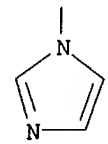


IT **290343-50-9P**, 8-[[2,6-Dichloro-3-[[2-(S)-[[4-(4-pyridinyl)-1-piperazinyl]carbonyl]-1-pyrrolidinyl]sulfonyl]phenyl]methoxy]-4-(1H-imidazol-1-yl)-2-methylquinoline tartrate **290343-52-1P**, 8-[[2,6-Dichloro-3-[[2-(S)-[[4-(2-pyridinyl)-1-piperazinyl]carbonyl]-1-pyrrolidinyl]sulfonyl]phenyl]methoxy]-4-(1H-imidazol-1-yl)-2-methylquinoline methanesulfonate **290344-03-5P**, 8-[[2,6-Dichloro-3-[[2-(S)-[[4-(2-pyridinyl)-1-piperazinyl]carbonyl]-1-pyrrolidinyl]sulfonyl]phenyl]methoxy]-2-methyl-4-(1H-1,2,4-triazol-1-yl)quinoline methanesulfonate **290344-05-7P**, 8-[[2,6-Dichloro-3-[[2-(S)-(4-morpholinylcarbonyl)-1-pyrrolidinyl]sulfonyl]phenyl]methoxy]-4-(1H-imidazol-1-yl)-2-methylquinoline tartrate **290344-07-9P**, 8-[[2,6-Dichloro-3-[[2-(S)-[(4-methyl-1-piperazinyl)carbonyl]-1-pyrrolidinyl]sulfonyl]phenyl]methoxy]-4-(1H-imidazol-1-yl)-2-methylquinoline tartrate **290344-09-1P**, 8-[[2,6-Dichloro-3-[[2-(S)-[(4-phenyl-1-piperazinyl)carbonyl]-1-pyrrolidinyl]sulfonyl]phenyl]methoxy]-4-(1H-imidazol-1-yl)-2-methylquinoline methanesulfonate **290344-21-7P**, 8-[[2,6-Dichloro-3-[[2-(S)-[[4-(2-pyridinylmethyl)-1-piperazinyl]carbonyl]-1-pyrrolidinyl]sulfonyl]phenyl]methoxy]-4-(1H-imidazol-1-yl)-2-methylquinoline methanesulfonate **290344-23-9P**, 8-[[2,6-Dichloro-3-[[2-(S)-[[4-(3-pyridinylmethyl)-1-piperazinyl]carbonyl]-1-pyrrolidinyl]sulfonyl]phenyl]methoxy]-4-(1H-imidazol-1-yl)-2-methylquinoline methanesulfonate **290344-25-1P**, 8-[[2,6-Dichloro-3-[[2-(S)-[[4-(4-pyridinylmethyl)-1-piperazinyl]carbonyl]-

1-pyrrolidinyl]sulfonyl]phenyl]methoxy]-4-(1H-imidazol-1-yl)-2-methylquinoline methanesulfonate
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(drug candidate; prepn. of heterocyclic benzenesulfonamide derivs. as bradykinin antagonists)

RN 290343-50-9 CAPLUS

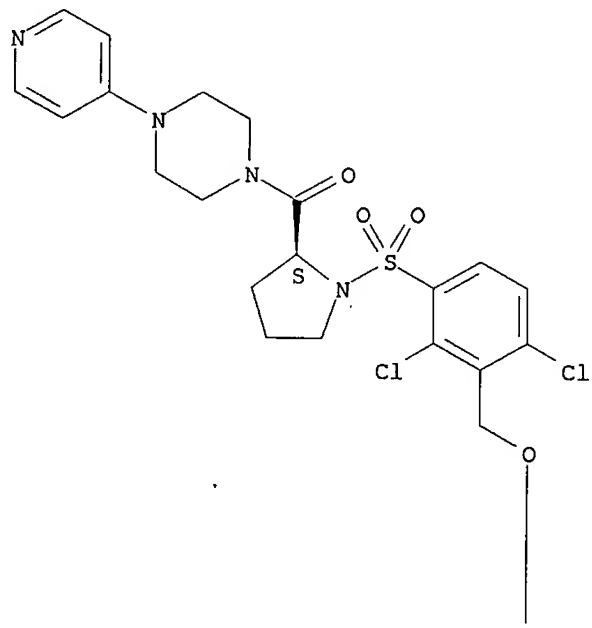
CN Piperazine, 1-[[(2S)-1-[[2,4-dichloro-3-[[[4-(1H-imidazol-1-yl)-2-methyl-8-quinolinyl]oxy]methyl]phenyl]sulfonyl]-2-pyrrolidinyl]carbonyl]-4-(4-pyridinyl)-, (2R,3R)-2,3-dihydroxybutanedioate (1:1) (9CI) (CA INDEX NAME)

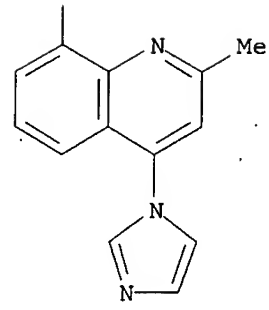
CM 1

CRN 290343-49-6
CMF C34 H33 Cl2 N7 O4 S

Absolute stereochemistry.

PAGE 1-A

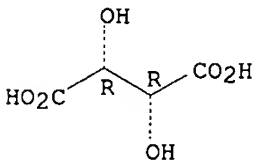




CM 2

CRN 87-69-4
CMF C4 H6 O6

Absolute stereochemistry.



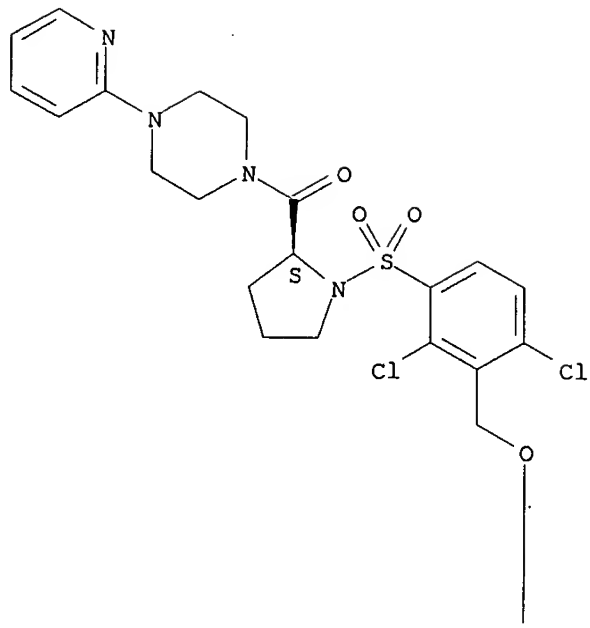
RN 290343-52-1 CAPLUS
CN Piperazine, 1-[[(2S)-1-[[2,4-dichloro-3-[[[4-(1H-imidazol-1-yl)-2-methyl-8-quinolinyl]oxy]methyl]phenyl]sulfonyl]-2-pyrrolidinyl]carbonyl]-4-(2-pyridinyl)-, monomethanesulfonate (9CI) (CA INDEX NAME)

CM 1

CRN 290343-51-0
CMF C34 H33 Cl2 N7 O4 S

Absolute stereochemistry.

PAGE 1-A



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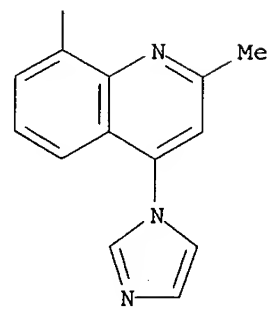
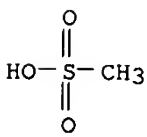


CM 2

CRN 75-75-2
CMF C H4 O3 S



RN 290344-03-5 CAPLUS
CN Piperazine, 1-[[(2S)-1-[[2,4-dichloro-3-[[[2-methyl-4-(1H-1,2,4-triazol-1-yl)-8-quinolinyl]oxy]methyl]phenyl]sulfonyl]-2-pyrrolidinyl]carbonyl]-4-(2-

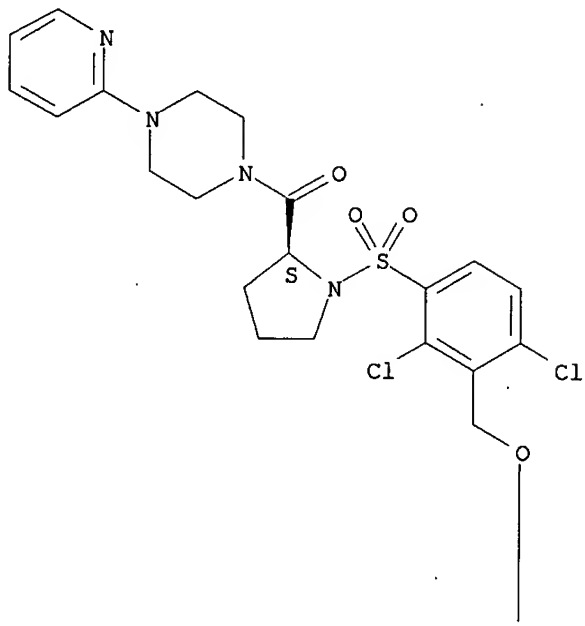
pyridinyl)-, monomethanesulfonate (9CI) (CA INDEX NAME)

CM 1

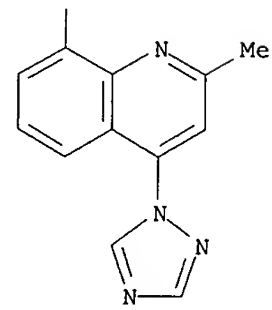
CRN 290344-02-4
CMF C33 H32 Cl2 N8 O4 S

Absolute stereochemistry.

PAGE 1-A

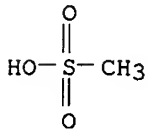


PAGE 2-A



CM 2

CRN 75-75-2
CMF C H4 O3 S



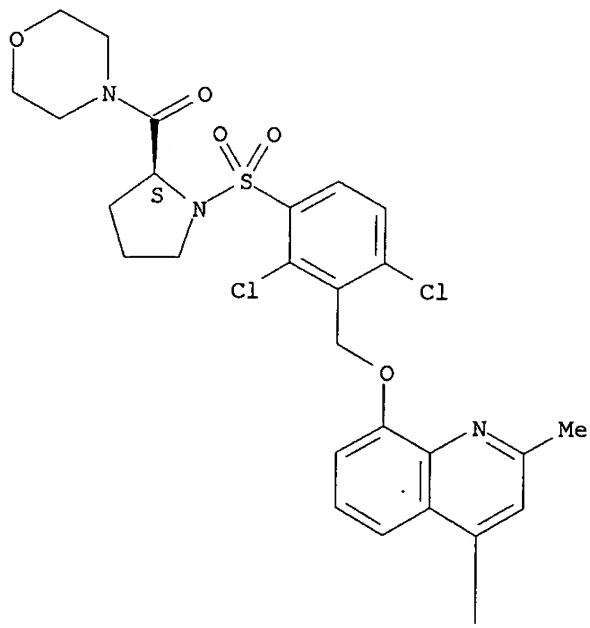
RN 290344-05-7 CAPLUS
CN Morpholine, 4-[[(2S)-1-[[2,4-dichloro-3-[[[4-(1H-imidazol-1-yl)-2-methyl-8-quinolinyl]oxy]methyl]phenyl]sulfonyl]-2-pyrrolidinyl]carbonyl]-, (2R,3R)-2,3-dihydroxybutanedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 290344-04-6
CMF C29 H29 Cl2 N5 O5 S

Absolute stereochemistry.

PAGE 1-A



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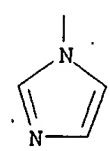
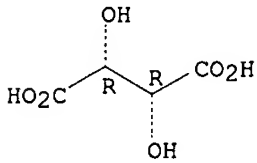


CM 2

CRN 87-69-4

CMF C4 H6 O6

Absolute stereochemistry.



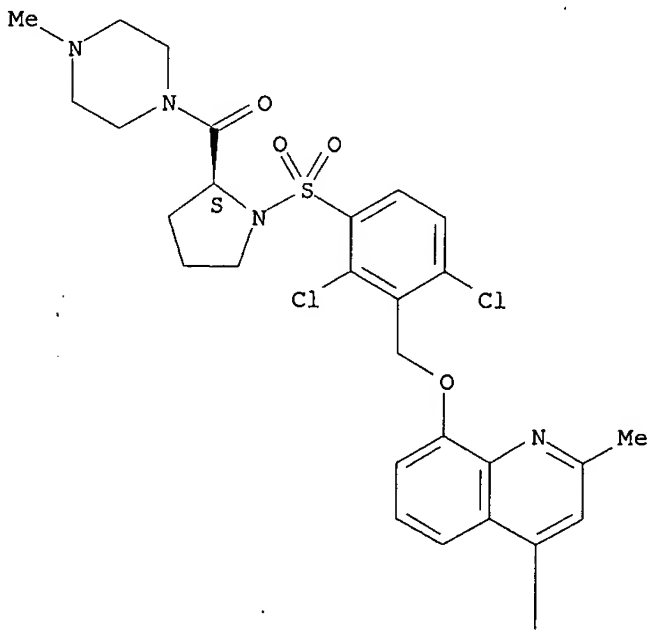
RN 290344-07-9 CAPLUS
CN Piperazine, 1-[[(2S)-1-[[2,4-dichloro-3-[[[4-(1H-imidazol-1-yl)-2-methyl-8-quinolinyl]oxy]methyl]phenyl]sulfonyl]-2-pyrrolidinyl]carbonyl]-4-methyl-, (2R,3R)-2,3-dihydroxybutanedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

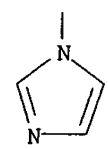
CRN 290344-06-8
CMF C30 H32 Cl2 N6 O4 S

Absolute stereochemistry.

PAGE 1-A



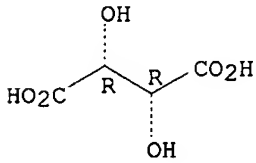
PAGE 2-A



CM 2

CRN 87-69-4
CMF C4 H6 O6

Absolute stereochemistry.



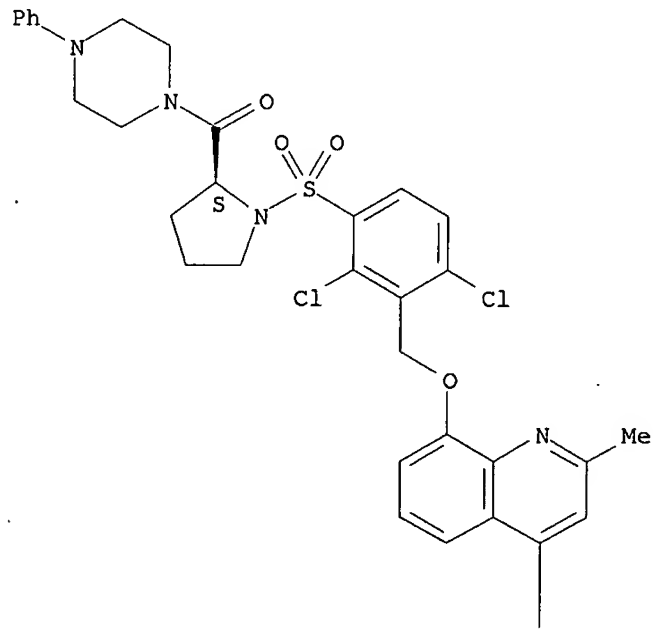
RN 290344-09-1 CAPLUS
CN Piperazine, 1-[[(2S)-1-[[2,4-dichloro-3-[[[4-(1H-imidazol-1-yl)-2-methyl-8-quinolinyl]oxy]methyl]phenyl]sulfonyl]-2-pyrrolidinyl]carbonyl]-4-phenyl-, monomethanesulfonate (9CI) (CA INDEX NAME)

CM 1

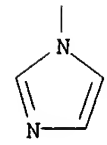
CRN 290344-08-0
CMF C35 H34 Cl2 N6 O4 S

Absolute stereochemistry.

PAGE 1-A

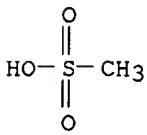


PAGE 2-A



CM 2

CRN 75-75-2
CMF C H4 O3 S



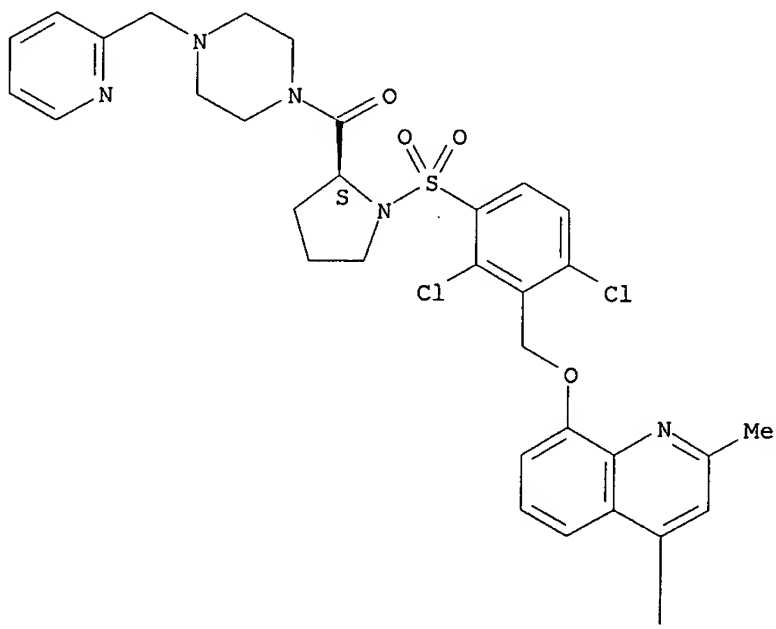
RN 290344-21-7 CAPLUS
CN Piperazine, 1-[[(2S)-1-[[2,4-dichloro-3-[[[4-(1H-imidazol-1-yl)-2-methyl-8-quinolinyl]oxy]methyl]phenyl]sulfonyl]-2-pyrrolidinyl]carbonyl]-4-(2-pyridinylmethyl)-, monomethanesulfonate (9CI) (CA INDEX NAME)

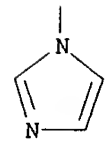
CM 1

CRN 290344-20-6
CMF C35 H35 Cl2 N7 O4 S

Absolute stereochemistry.

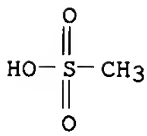
PAGE 1-A





CM 2

CRN 75-75-2
CMF C H4 O3 S



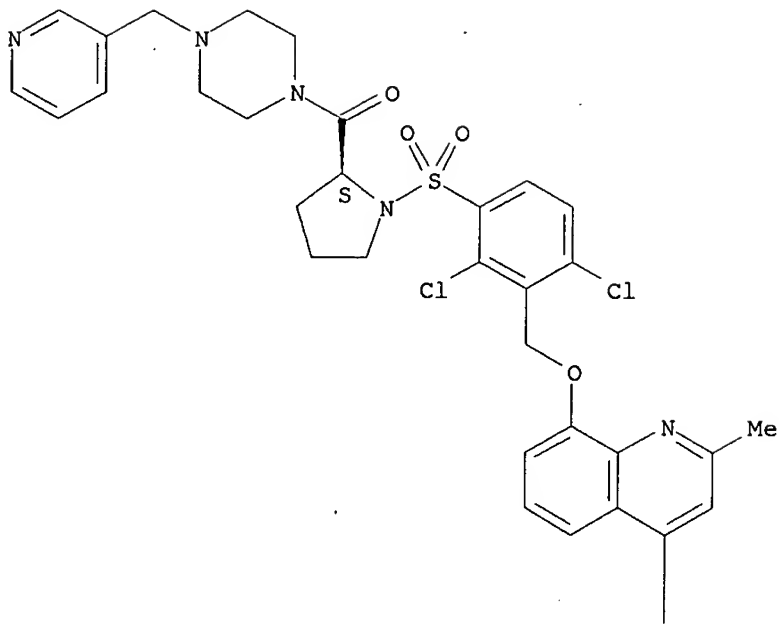
RN 290344-23-9 CAPLUS
CN Piperazine, 1-[[(2S)-1-[[2,4-dichloro-3-[[[4-(1H-imidazol-1-yl)-2-methyl-8-quinolinyl]oxy]methyl]phenyl]sulfonyl]-2-pyrrolidinyl]carbonyl]-4-(3-pyridinylmethyl)-, monomethanesulfonate (9CI) (CA INDEX NAME)

CM 1

CRN 290344-22-8
CMF C35 H35 Cl2 N7 O4 S

Absolute stereochemistry.

PAGE 1-A



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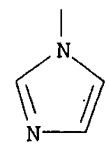
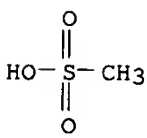


CM 2

CRN 75-75-2
CMF C H4 O3 S



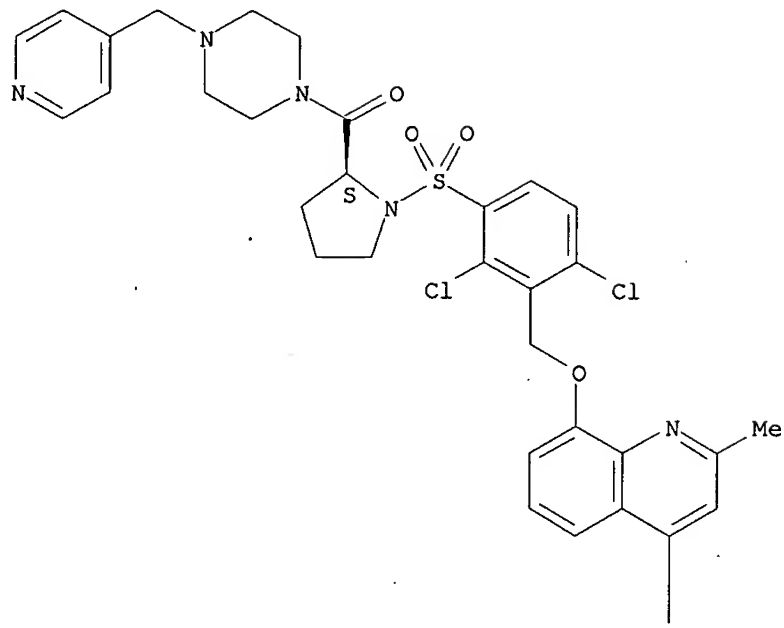
RN 290344-25-1 CAPLUS
CN Piperazine, 1-[[(2S)-1-[[2,4-dichloro-3-[[[4-(1H-imidazol-1-yl)-2-methyl-8-quinolinyl]oxy]methyl]phenyl]sulfonyl]-2-pyrrolidinyl]carbonyl]-4-(4-pyridinylmethyl)-, monomethanesulfonate (9CI) (CA INDEX NAME)

CM 1

CRN 290344-24-0
CMF C35 H35 Cl2 N7 O4 S

Absolute stereochemistry.

PAGE 1-A



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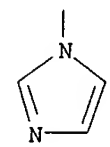
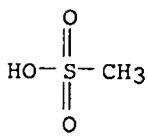


CM 2

CRN 75-75-2
CMF C H4 O3 S

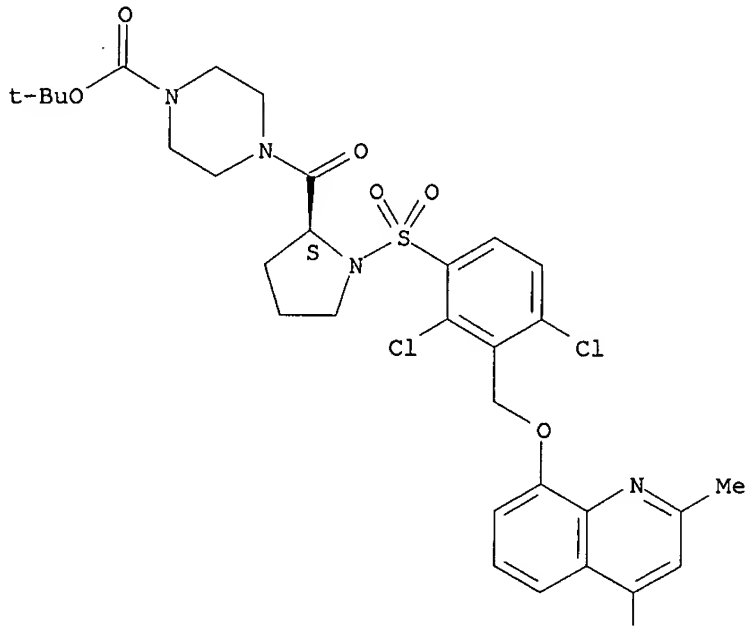


IT **290345-24-3P**, 4-[[1-[[2,4-Dichloro-3-[[[4-(1H-imidazol-1-yl)-2-methyl-8-quinolinyl]oxy]methyl]phenyl]sulfonyl]-2-(S)-pyrrolidinyl]carbonyl]-1-piperazinecarboxylic acid 1,1-dimethylethyl ester
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; prepn. of heterocyclic benzenesulfonamide derivs. as bradykinin antagonists)

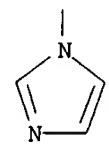
RN 290345-24-3 CAPLUS
CN 1-Piperazinecarboxylic acid, 4-[[(2S)-1-[[2,4-dichloro-3-[[[4-(1H-imidazol-1-yl)-2-methyl-8-quinolinyl]oxy]methyl]phenyl]sulfonyl]-2-pyrrolidinyl]carbonyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 2-A



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 8 OF 12 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1999:99155 CAPLUS
DOCUMENT NUMBER: 130:306868
TITLE: In vitro and in vivo effects of the new nonpeptide bradykinin B2 receptor antagonist, LF 16-0335C, on guinea pig and rat kinin receptors
AUTHOR(S): Pruneau, Didier; Luccarini, Jean-Michel; Fouchet, Chantal; Defrene, Evelyne; Franck, Rose-Marie; Loillier, Bruno; Duclos, Herve; Robert, Claude; Cremers, Beatrice; Belichard, Pierre; Paquet, Jean-Luc
CORPORATE SOURCE: Groupe de Pharmacochimie des Recepteurs, Centre de Recherche, Laboratories Fournier, Daix, 21121, Fr.
SOURCE: Fundamental & Clinical Pharmacology (1999), 13(1), 75-83

CODEN: FCPHEZ; ISSN: 0767-3981
PUBLISHER: Editions Scientifiques et Medicales Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Activation of the kinin-kallikrein system and stimulation of bradykinin (BK) B2 receptors are thought to play an important role in the pathophysiol. of inflammation and pain. In the present study, we report the pharmacol. properties of a novel nonpeptide bradykinin B2 receptor antagonist, LF 16-0335C, (1-[[3-[(2,4-dimethylquinolin-8-yl)oxymethyl]-2,4-dichloro-phenyl]sulfonyl]-2(S)-[[4-[4-(aminoiminomethyl)-phenylcarbonyl]piperazin-1-yl]carbonyl]pyrrolidine, 2HCl). In binding studies, LF 16-0335C competed with [3H]bradykinin giving Ki values of 1.65 .+-. 0.36 nM and 2.20 .+-. 0.30 nM in membrane prepns. from rat uterus (RU) and guinea pig ileum (GPI), resp. In functional expts., LF 16-0335C inhibited in a competitive manner BK-induced contractions of both isolated RU and GPI, leading to calcd. pA2 values of 7.70 .+-. 0.70 and 8.30 .+-. 0.30, resp. The inhibitory effect of LF 16-0335C was fully reversible by washing in the guinea pig ileum. In vivo, LF 16-0335C given i.v. inhibited in a dose-dependent manner BK-induced hypotension in both animal species, although it was more potent in the guinea pig than in the rat (ED50, 2.5 .+-. 1.6 .mu.g/kg vs. 22.6 .+-. 2.3 .mu.g/kg). BK is a potent constrictor of guinea pig airways and this effect was markedly attenuated by LF 16-0335C. In contrast, LF 16-0335C did not affect histamine- and acetylcholine-induced hypotensive response in the rat. We conclude that LF 16-0335C is a potent and selective nonpeptide B2 receptor antagonist which equally binds to the rat and guinea pig receptor but displays a different in vivo potency in the two species. Therefore, this drug represents a useful tool to better assess the role of bradykinin in pathophysiol. conditions.

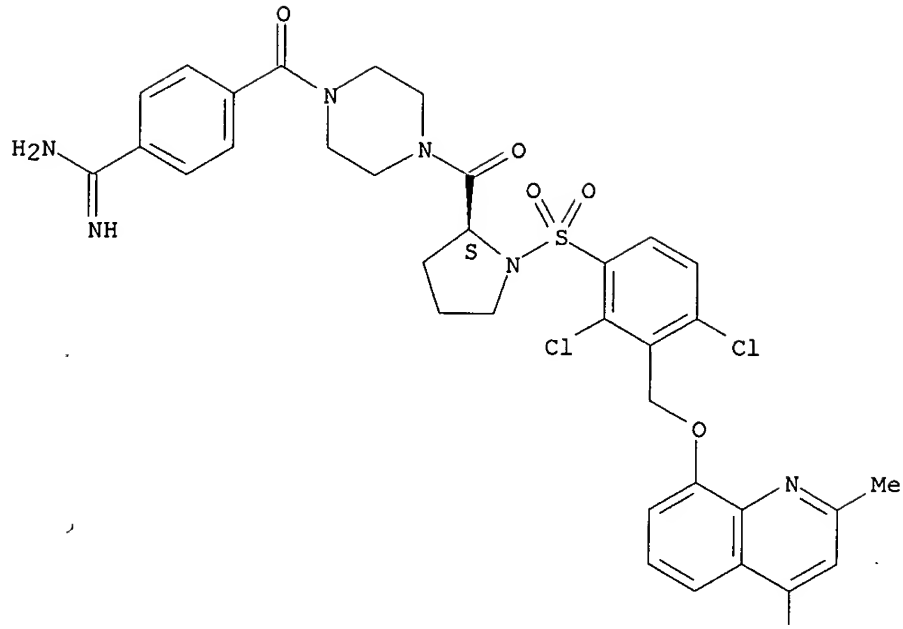
IT **202720-59-0**, LF 16-0335C
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(nonpeptide bradykinin B2 receptor antagonist LF 16-0335C effects on guinea pig and rat kinin receptors)

RN 202720-59-0 CAPLUS

CN Piperazine, 1-[4-(aminoiminomethyl)benzoyl]-4-[[(2S)-1-[[2,4-dichloro-3-[[(2,4-dimethyl-8-quinolinyl)oxy]methyl]phenyl]sulfonyl]-2-pyrrolidinyl]carbonyl]-, dihydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

PAGE 1-A



PAGE 2-A

●2 HCl

REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 9 OF 12 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1999:36652 CAPLUS
DOCUMENT NUMBER: 130:205272
TITLE: Constitutive activation of the human bradykinin B2 receptor induced by mutations in transmembrane helices III and VI
AUTHOR(S): Marie, Jacky; Koch, Caroline; Pruneau, Didier; Paquet, Jean-Luc; Groblewski, Thierry; Larguier, Renee; Lombard, Colette; Deslauriers, Benoit; Maigret, Bernard; Bonnafous, Jean-Claude
CORPORATE SOURCE: Institut National de la Sante et de la Recherche Medicale U 439, Montpellier, 34090, Fr.
SOURCE: Molecular Pharmacology (1999), 55(1), 92-101
CODEN: MOPMA3; ISSN: 0026-895X
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We report that mutation of specific residues in the human B2 bradykinin

(BK) receptor induces its marked constitutive activation, evaluated through inositol phosphate prodn. in COS-7 cells expressing the wild-type or mutant receptors. We provide evidence for a strikingly high constitutive activation of the B2 receptor induced by alanine substitution of the Asn113 residue, located in the third transmembrane domain. These results are reminiscent of our previous finding that mutation of the homologous Asn111 residue induces constitutive activation of the AT1 angiotensin II receptor. BK overstimulation of the constitutively activated mutant N113A receptor was also obsd. Phe replacement of the Trp256 residue, fairly conserved in transmembrane domain VI of G protein-coupled receptors, also induced a less prominent but significant constitutive activation. Interestingly, the peptidic HOE 140 compd. and an original nonpeptidic compd. LF 160335, which both behaved as inverse agonists of the wild-type receptor expressed in COS-7 cells, became potent and efficient agonists of the two constitutively activated mutant N113A and W256F receptors. These parallel changes obsd. for two chem. unrelated series can serve as a basis for future studies of structure-function relationships and modeling of activation processes, based on a detailed anal. of the network of helix-helix interactions, which stabilize the inactive receptor conformation and undergo rearrangements on transition to activated states.

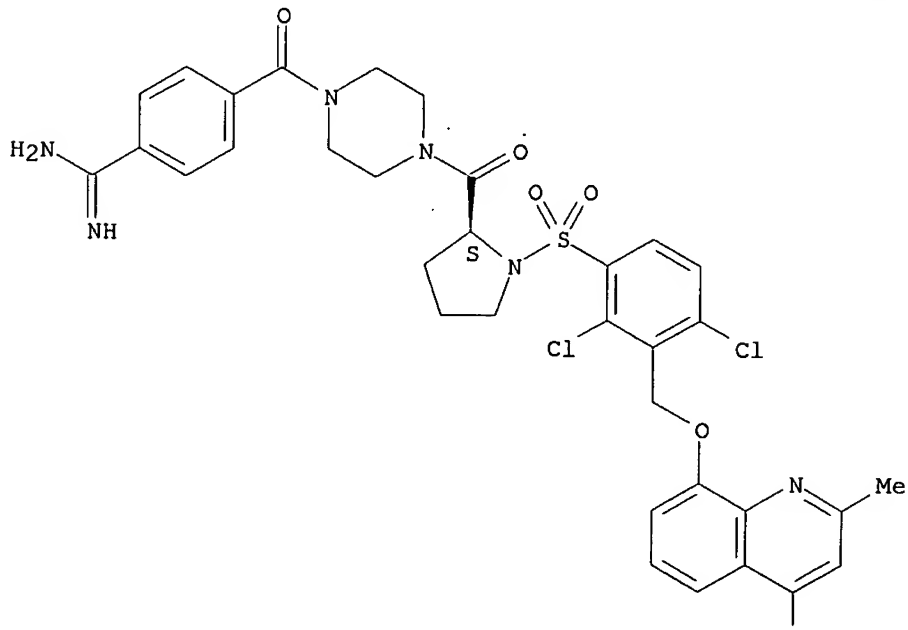
IT **202602-34-4**, LF 160335
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(HOE 140 and LF 160335 as potent agonists for human bradykinin B2 receptor with transmembrane helixes III and VI mutations inducing constitutive activation)

RN 202602-34-4 CAPLUS

CN Piperazine, 1-[4-(aminoiminomethyl)benzoyl]-4-[[(2S)-1-[[2,4-dichloro-3-[[(2,4-dimethyl-8-quinolinyl)oxy]methyl]phenyl]sulfonyl]-2-pyrrolidinyl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

PAGE 1-A



PAGE 2-A

Me

REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 10 OF 12 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1998:634689 CAPLUS
DOCUMENT NUMBER: 129:339848
TITLE: LF 16.0335, a novel potent and selective nonpeptide antagonist of the human bradykinin B2 receptor
AUTHOR(S): Pruneau, Didier; Luccarini, Jean-Michel; Fouchet, Chantal; Defrene, Evelyne; Franck, Rose-Marie; Loillier, Bruno; Duclos, Herve; Robert, Claude; Cremers, Beatrice; Belichard, Pierre; Paquet, Jean-Luc
CORPORATE SOURCE: Groupe de Pharmacochimie des Recepteurs, Centre de Recherche, Laboratoires Fournier, Daix, 21121, Fr.
SOURCE: British Journal of Pharmacology (1998), 125(2), 365-372
CODEN: BJPCBM; ISSN: 0007-1188
PUBLISHER: Stockton Press
DOCUMENT TYPE: Journal
LANGUAGE: English

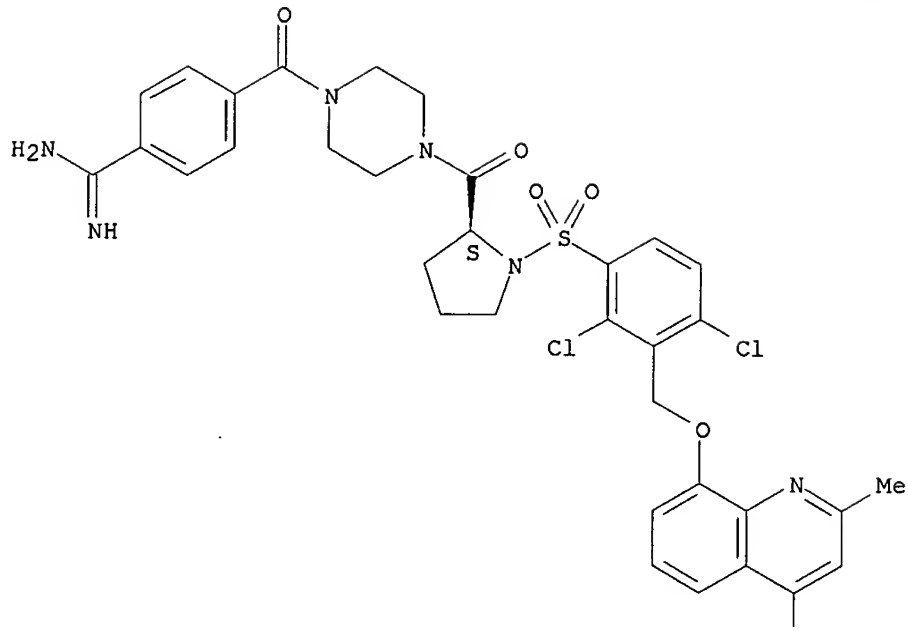
AB In the present paper, we describe the in vitro pharmacol. properties of LF 16.0335 (1-[[3-[(2,4-dimethylquinolin-8-yl)oxymethyl]-2,4-dichlorophenyl]sulfonyl]-2(S)-[[4-[4-(aminoiminomethyl)phenylcarbonyl]piperazin-1-yl]carbonyl]pyrrolidine), a novel and potent nonpeptide antagonist of the human bradykinin (BK) B2 receptor. LF 16.0335 displaced [3H]-BK binding to membrane prepns. from CHO cells expressing the cloned human B2 receptor, INT 407 cells and human umbilical vein with Ki values of 0.84.+-.0.39 nM, 1.26.+-.0.68 nM and 2.34.+-.0.36 nM, resp. In satn. binding studies performed in INT 407 cell membranes in the presence or absence of LF 16.0335, Bmax values of [3H]-BK were not significantly changed suggesting that LF 16.0335 behaves as a competitive antagonist. LF 16.0335 had no affinity for the cloned human kinin B1 receptor stably expressed in 293 cells. In addn., this compd. at 1 .mu.M did not significantly bind to a range of 40 different membrane receptors and eight ion channels except muscarinic M2 and M1 receptors for which an IC50 value of 0.9 and 1 .mu.M was obtained. BK stimulates in a concn.-dependent manner phosphoinositides (IPs) prodn. in cultured INT 407 cells. Concn.-response-curves to BK were shifted to the right in the presence of LF 16.0335 (0.1 .mu.M) without redn. of the max. LF 16.0335 inhibited the concn.-contraction curve to BK in the human umbilical vein giving a pA2 value of 8.30.+-.0.30 with a Schild plot slope that was not different from unity. These results demonstrate that LF 16.0335 is a potent, selective and competitive antagonist of the human bradykinin B2 receptor.

IT **202602-34-4**, LF 160335
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(LF 16.0335, a novel potent and selective nonpeptide antagonist of the human bradykinin B2 receptor)

RN 202602-34-4 CAPLUS
CN Piperazine, 1-[4-(aminoiminomethyl)benzoyl]-4-[[(2S)-1-[[2,4-dichloro-3-[[(2,4-dimethyl-8-quinolinyl)oxy]methyl]phenyl]sulfonyl]-2-pyrrolidinyl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

PAGE 1-A



PAGE 2-A

REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 11 OF 12 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1998:87728 CAPLUS
DOCUMENT NUMBER: 128:154381
TITLE: Preparation of N-benzenesulfonyl-L-proline derivatives as bradykinin B2 agonists
INVENTOR(S): Dodey, Pierre; Bondoux, Michel; Houziaux, Patrick; Barth, Martine; Ou, Khan
PATENT ASSIGNEE(S): Fournier Industrie et Sante, Fr.; Dodey, Pierre; Bondoux, Michel; Houziaux, Patrick; Barth, Martine; Ou, Khan
SOURCE: PCT Int. Appl., 72 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9803503	A1	19980129	WO 1997-FR1377	19970723

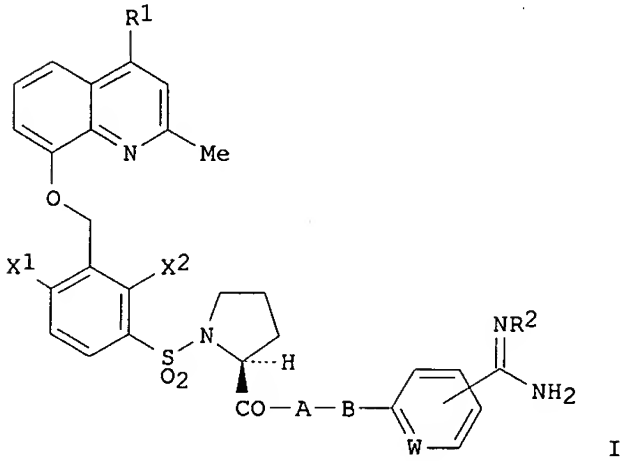
W: AU, BG, BR, CA, CN, CZ, EE, HU, IL, JP, KR, MX, NO, NZ, PL, RO, RU, SG, SK, TR, UA, US, VN
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

FR 2751650	A1	19980130	FR 1996-9327	19960724
FR 2751650	B1	19981009		
CA 2261743	AA	19980129	CA 1997-2261743	19970723
AU 9738536	A1	19980210	AU 1997-38536	19970723
EP 925295	A1	19990630	EP 1997-935612	19970723
EP 925295	B1	20011004		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, RO				
JP 2000514818	T2	20001107	JP 1998-506663	19970723
AT 206419	E	20011015	AT 1997-935612	19970723
ES 2167768	T3	20020516	ES 1997-935612	19970723
US 6071917	A	20000606	US 1999-230334	19990125

PRIORITY APPLN. INFO.: FR 1996-9327 A 19960724
WO 1997-FR1377 W 19970723

OTHER SOURCE(S): MARPAT 128:154381

GI



I

AB N-benzenesulfonyl-L-proline derivs. I [X1, X2 = halo, alkoxy; R1 = H, trifluoroalkyl, alkyl; R2 = H, OH; A = NR3(CH2)n (R3 = H, Me and n = 0-3), 1,4-piperazinediyl, hexahydro-1,4-diazepine-1,4-diyl, NH(CH2)nCH(CH2CH2)2N [n = 0-3, CH(CH2CH2)2N = 1,4-piperazinediyl]; B = bond, CO, COCH2, COCH2O, COCH:CH, SO2; W = CH, N] or their salts were prepd. as bradykinin B2 agonists. Thus, I.2HCl (X1 = X2 = Cl, R1 = Me, R2 = H, A = NHCH2, B = bond, W = CH; the amidino group is in the 3-position) was prepd. from N-[[3-[(2,4-dimethylquinolin-8-yl)oxymethyl]-2,4-dichlorophenyl]sulfonyl]-L-proline by sequential reaction with H2S, MeI, NH4OAc, and HCl. The product inhibited binding of [3H] bradykinin to the B2 receptor in guinea pigs (100% activity).

IT **202602-67-3P 202602-76-4P 202602-78-6P**
202602-82-2P 202602-85-5P 202602-89-9P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(prepn. of benzenesulfonylproline derivs. as bradykinin B2 agonists)

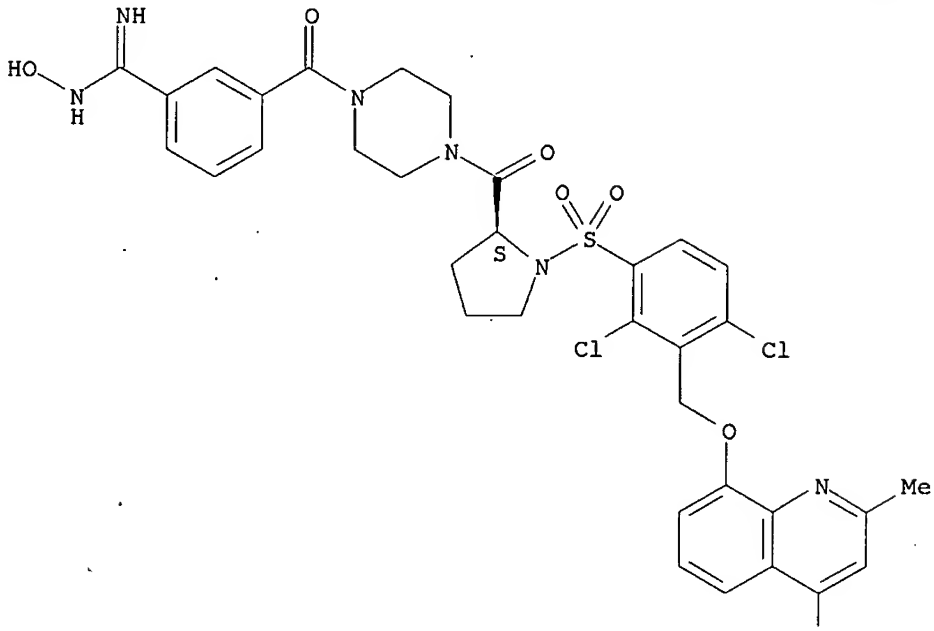
RN 202602-67-3 CAPLUS

CN Piperazine, 1-[[(2S)-1-[[2,4-dichloro-3-[[(2,4-dimethyl-8-quinolinyl)oxy]methyl]phenyl]sulfonyl]-2-pyrrolidinyl]carbonyl]-4-[3-

[(hydroxyamino)iminomethyl]benzoyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

PAGE 1-A



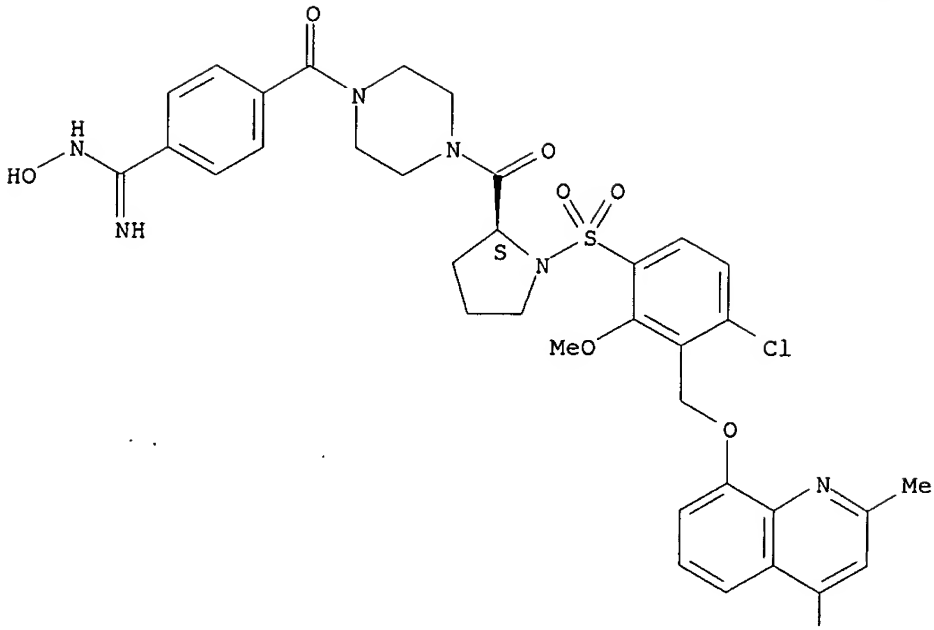
PAGE 2-A

RN 202602-76-4 CAPLUS

CN Piperazine, 1-[[(2S)-1-[[4-chloro-3-[[(2,4-dimethyl-8-quinolinyl)oxy]methyl]-2-methoxyphenyl]sulfonyl]-2-pyrrolidinyl]carbonyl]-4-[4-[(hydroxyamino)iminomethyl]benzoyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

PAGE 1-A

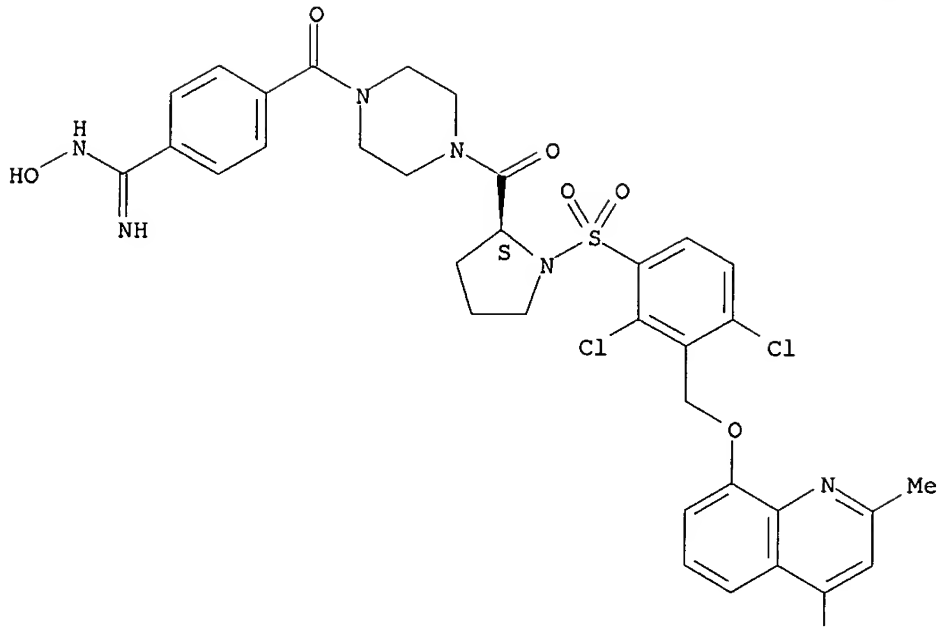


PAGE 2-A

RN 202602-78-6 CAPLUS
CN Piperazine, 1-[[(2S)-1-[[2,4-dichloro-3-[[[2-methyl-4-(trifluoromethyl)-8-quinolinyl]oxy]methyl]phenyl]sulfonyl]-2-pyrrolidinyl]carbonyl]-4-[4-[(hydroxyamino)iminomethyl]benzoyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

PAGE 1-A

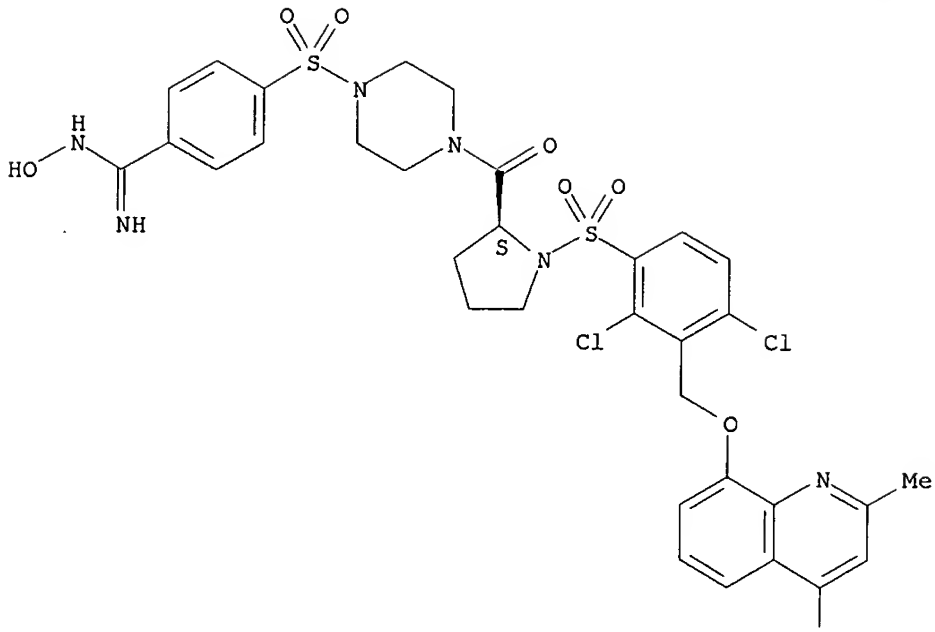


PAGE 2-A

RN 202602-82-2 CAPLUS
CN Piperazine, 1-[[(2S)-1-[[2,4-dichloro-3-[[(2,4-dimethyl-8-quinolinyl)oxy]methyl]phenyl]sulfonyl]-2-pyrrolidinyl]carbonyl]-4-[[4-[(hydroxyamino)iminomethyl]phenyl]sulfonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

PAGE 1-A



PAGE 2-A

RN 202602-85-5 CAPLUS
CN Piperazine, 1-[[(1S)-1-[[2,4-dichloro-3-[[(2,4-dimethyl-8-quinolinyl)oxy]methyl]phenyl]sulfonyl]-2-pyrrolidinyl]carbonyl]-4-[[5-[(hydroxyamino)iminomethyl]-2-pyridinyl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

US 20020128271A1

(19) United States

(12) Patent Application Publication (10) Pub. No.: US 2002/0128271 A1

Katsu et al. (43) Pub. Date: Sep. 12, 2002

(54) N-BENZENESULFONYL L-PROLINE COMPOUNDS AS BRADYKININ ANTAGONISTS

(75) Inventors: Yasuhiro Katsu, Tokyo (JP); Makoto Kawai, Tokyo (JP); Hiroki Koike, Tokyo (JP); Seiji Nukui, Tokyo (JP)

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5TH FLOOR - STOP 49
NEW YORK, NY 10017-5612 (US)

(73) Assignee: Pfizer Inc.

(21) Appl. No.: 10/010,863

(22) Filed: Dec. 5, 2001

Related U.S. Application Data

(60) Provisional application No. 60/251,225, filed on Dec. 5, 2000.

Publication Classification

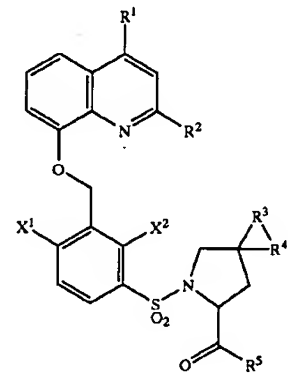
(51) Int. Cl.[7] A61K 31/496; A61K 31/4709; C07D 43/02; C07D 43/14

(52) U.S. Cl. 514/253.06; 514/314; 544/362; 544/363; 546/176

(57) ABSTRACT

This invention provides a compound of the formula (I):

(I)



or the pharmaceutically acceptable salts thereof wherein X^1 and X^2 are halo; R^1 and R^2 are independently hydrogen or C_{1-4} alkyl; R^3 and R^4 are each hydrogen or halo; and

R^5 is

(a) —C_{3-9} diazacycloalkyl optionally substituted with C_{5-11} azabicycloalkyl;

(b) —C_{3-9} azacycloalkyl-NH—(C_{5-11} azabicycloalkyl optionally substituted with C_{1-4} alkyl);

(c) —NH—C_{1-3} alkyl-C(O)—C_{5-11} diazabicycloalkyl;

(d) —NH—C_{1-3} alkyl-C(O)—NH—C_{5-11} azabicycloalkyl, the C_{5-11} azabicycloalkyl being optionally substituted with C_{1-4} alkyl;

(e) —C_{3-9} azacycloalkyl optionally substituted with C_{3-9} azacycloalkyl; or

(f) —NH—C_{1-5} alkyl-NH—C(O)—C_{4-9} cycloalkyl-NH_2.

These compounds are useful for the treatment of medical conditions mediated by bradykinin such as inflammation, allergic rhinitis, pain, etc. This invention also provides a pharmaceutical composition comprising the above compound.

N-BENZENESULFONYL L-PROLINE COMPOUNDS AS BRADYKININ ANTAGONISTS

TECHNICAL FIELD

[0001] This invention relates to novel N-benzenesulfonyl L-proline compounds. These compounds are useful as antagonists of bradykinin, and are thus useful in the treatment of inflammation, asthma, allergic rhinitis, pain or the like in mammalian, especially humans. The present invention also relates to a pharmaceutical composition comprising the above compounds.

BACKGROUND ART

[0002] Bradykinin ("BK") is generated under normal conditions in mammalia by the action of various plasma enzymes such as kallikrein on high molecular weight kininogens. It is widely distributed in mammals, and relates its two receptor subtypes, B_1 and B_2. The actions of BK at the B_2 receptor include mainly contraction of arterial and venous preparations, although it can cause relaxation of peripheral resistance vessels as well.

[0003] Many of the more important functions of BK, such as increases in vascular permeability, pain, and vasodilatation, however, are mediated by the B_2 receptor. These effects at the B_2 receptor are believed to be responsible for BK's role in numerous diseases, such as inflammation, cardiovascular disease, pain, and the common cold. Hence antagonists at the B_2 receptor should find considerable therapeutic applications. Most of the efforts in this area thus far have been directed at peptidic analogues of the BK structure, some of which have been studied as analgesics and antiinflammatory agents.

[0004] Numerous N-benzenesulfonyl L-proline compounds as a B_2 antagonist have been synthesized, and disclosed in a number of patent publications such as international publication Nos. WO 97/41104, WO 96/13485, WO 99/00387, WO 98/24783, WO 98/03503, WO 97/24349, WO 97/07115 and WO 96/40639.

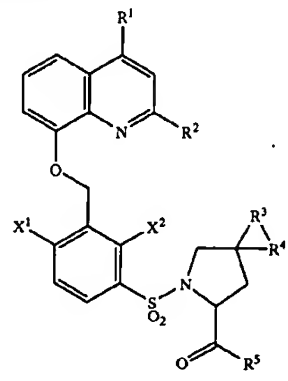
[0005] International Publication Number WO 98/24783, WO 98/03503, WO 97/24349, WO 97/07115 disclose a variety of N-benzenesulfonyl L-proline compounds as antagonists of bradykinin.

[0006] It would be desirable if there were provided a non-peptide antagonist of the B_2 receptor, having an improved B_2 antagonistic activity and a good metabolic stability against human liver microsomes.

BRIEF DISCLOSURE OF THE INVENTION

[0007] The present invention provides a compound of the following formula:

(I)



[0008] or the pharmaceutically acceptable salts thereof wherein

[0009] X^1 and X^2 are independently halo or C_{1-4} alkyl;

[0010] R^1 and R^2 are independently hydrogen or C_{1-4} alkyl;

[0011] R^3 and R^4 are independently hydrogen or halo; and

[0012] R^5 is

[0013] (a) —C_{3-9} diazacycloalkyl optionally substituted with C_{5-11} azabicycloalkyl;

[0014] (b) —C_{3-9} azacycloalkyl-NH—(C_{5-11}, azabicycloalkyl optionally substituted with C_{1-4} alkyl);

[0015] (c) —NH—C_{1-3} alkyl-C(O)—C_{5-11} diazabicycloalkyl;

[0016] (d) —NH—C_{1-3} alkyl-C(O)—NH—C_{5-11} azabicycloalkyl, the C_{5-11} azabicycloalkyl being optionally substituted with C_{1-4} alkyl;

[0017] (e) —C_{3-9} azacycloalkyl optionally substituted with C_{3-9} azacycloalkyl; or

[0018] (f) —NH—C_{1-5} alkyl-NH—C(O)—C_{4-9} cycloalkyl-NH_2.

[0019] The N-benzenesulfonyl L-proline compounds of this invention have an antagonistic action towards bradykinin and are thus useful in therapeutics, particularly for the treatment of inflammation, rheumatoid arthritis, cystitis, post-traumatic and post ischemic cerebral edema, liver cirrhosis, Alzheimer's disease, cardiovascular disease, pain, common cold, allergies, asthma, pancreatitis, burns, virus infection, head injury, multiple trauma, rhinitis, hepatorenal failure, diabetes, metastasis, pancreatitis, neovascularization, corneal haze, glaucoma, ocular pain, ocular hypertension or the like in mammalian, especially humans.

[0020] The N-benzenesulfonyl L-proline compounds of this invention have an antagonistic action towards bradykinin and are thus useful in therapeutics, particularly for the treatment of Amyotrophic lateral sclerosis, Huntington's disease, Parkinson's disease, multiple sclerosis, stroke, head trauma, post-surgical brain edema, brain edema (general), cytotoxic brain edema (such as that associated with brain tumors, stroke, head trauma, etc.), brain edema associated with metabolic diseases (renal failure, pediatric metabolic diseases, etc.), rheumatoid arthritis, osteoarthritis, migraine, neuropathic pain, pruritis, brain tumor, pseudotumor cerebri, glaucoma, hydrocephalus, spinal cord trauma, spinal cord edema, neurodegenerative diseases, respiratory diseases, diuresis, natriuresis calciuresis, COPD (chronic obstructive pulmonary disease), post-traumatic brain injury, itching, sepsis or the like in mammalian, especially humans.

[0021] The present invention provides a pharmaceutical composition for the treatment of disease conditions mediated by bradykinin, in a mammalian subject, which com-

prises administering to said subject a therapeutically effective amount of a compound of formula (I).

[0022] Further, the present invention also provides a pharmaceutical composition for the treatment of inflammation, rheumatoid arthritis, cystitis, post-traumatic and post ischemic cerebral edema, liver cirrhosis, Alzheimer's disease, cardiovascular disease, pain, common cold, allergies, asthma, pancreatitis, burns, virus infection, head injury, multiple trauma, rhinitis, hepatorenal failure, diabetes, metastasis, pancreatitis, neovascularization, corneal haze, glaucoma, ocular pain, ocular hypertension or the like, which comprises a therapeutically effective amount of the N-benzenesulfonyl L-proline compound of formula (I) or its pharmaceutically acceptable salt together with a pharmaceutically acceptable carrier.

[0023] Further, the present invention also provides a pharmaceutical composition for the treatment of Amyotrophic lateral sclerosis, Huntington's disease, Parkinson's disease, Multiple sclerosis, Stroke, head trauma, Post-surgical brain edema, Brain edema (general), Cytotoxic brain edema (such as that associated with brain tumors, stroke, head trauma, etc.), Brain edema associated with metabolic diseases (renal failure, pediatric metabolic diseases, etc.), Rheumatoid arthritis, Osteoarthritis, Migraine, Neuropathic Pain, Pruritis, Brain Tumor, Pseudotumor cerebri, Glaucoma, Hydrocephalus, Spinal cord trauma, Spinal cord edema, neurodegenerative diseases, respiratory diseases, diuresis, natriuresis calciuresis, COPD (chronic obstructive pulmonary disease), post-traumatic brain injury, itching or Sepsis, which comprises a therapeutically effective amount of a compound of formual (I) or its pharmaceutically acceptable carrier.

[0024] Also, the present invention provides a method for the treatment of disease conditions mediated by bradykinin, in a mammalian subject, which comprises administering to said subject a therapeutically effective amount of a compound of formula (I).

[0025] Further, the present invention provides a method for the treatment of inflammation, rheumatoid arthritis, cystitis, post-traumatic and post ischemic cerebral edema, liver cirrhosis, Alzheimer's disease, cardiovascular disease, pain, common cold, allergies, asthma, pancreatitis, burns, virus infection, head injury, multiple trauma, rhinitis, hepatorenal failure, diabetes, metastasis, pancreatitis, neovascularization, corneal haze, glaucoma, ocular pain, ocular hypertension or the like, in a mammalian subject, which comprises administering to said subject a therapeutically effective amount of a compound of formula (I).

DETAILED DESCRIPTION OF THE INVENTION

[0026] As used herein, the term "halo" is fluoro, chloro, bromo or iodo (preferably fluoro or chloro).

[0027] As used herein, the term "alkyl" means straight or branched chain saturated radicals, including, but not limited to methyl, ethyl, n-propyl, isopropyl, n-butyl, iso-butyl, secondary-butyl, tertiary-butyl.

[0028] As used herein, the term "C_{4-9} cycloalkyl" means monocyclic alkyl having 4 to 9 carbon atoms, such as cyclobutyl, cyclopentyl, cycloheptyl, cyclohexyl, and the like.

[0029] As used herein, the term "C_{3-9} azacycloalkyl, C_{3-9} diazacycloalkyl, C_{5-11} azabicycloalkyl or C_5-11 diazabicycloalkyl "means a group wherein one or two carbons of mono- or bicyclic alkyl ring components are substituted by nitrogen atoms, included, but not limited to, azetidinyl, piperazinyl, piperidino, piperidinyl, pyrrolidinyl, azabicyclo [3.3.0]octyl, quinuclidinyl, azabicyclo[3.2.1]octyl, azabicyclo[3.3.1]nonyl, azabicyclo[2.2.2]octyl or diazabicyclo [3.2.1]octyl.

[0030] In the formula (I), R^5 is preferably (a) —C_{3-9} diazacycloalkyl optionally substituted with C_{5-11} azabicycloalkyl or (c) —NH—C_{1-3} alkyl-C(O)—C_{5-11} diazabicycloalkyl, more preferably (a) —C_{4-8} diazacycloalkyl optionally substituted with C_{6-10} azabicycloalkyl or —NH—C_{1-3} alkyl-C(O)—C_{6-10} diazabicycloalkyl, further preferably azabicyclo[2.2.2]octyl-piperazinyl, diazabicyclo[3.2.1]octyl-oxomethylamino or diazabicyclo[3.2.1]octyl-oxoethylamino, and most preferably azabicyclo[2.2.2]octyl-piperazinyl or diazabicyclo[3.2.1]octyl-oxomethylamino.

[0031] Preferred compounds of this invention are those of the formula (I) wherein

[0032] X^1 and X^2 are chloro;

[0033] R^1 and R^2 are independently hydrogen, methyl or ethyl;

[0034] R^3 and R^4 are independently hydrogen or fluoro; and

[0035] R^5 is

[0036] (a) —C_{4-8} diazacycloalkyl optionally substituted with C_{6-10} azabicycloalkyl;

[0037] (b) —C_{3-6} azacycloalkyl-NH—(C_{6-10} azabicycloalkyl optionally substituted with C_{1-4} alkyl);

[0038] (c) —NH—C_{1-3} alkyl-C(O)—C_{6-10} diazabicycloalkyl;

[0039] (d) —NH—C_{1-3} alkyl-C(O)—NH—C_{6-10} azabicycloalkyl, the C_{6-10} azabicycloalkyl being optionally substituted with C_{1-4} alkyl;

[0040] (e) —C_{4-8} azacycloalkyl optionally substituted with C_{4-8} azacycloalkyl; or

[0041] (f) —NH—C_{1-5} alkyl-NH—C(O)—C_{5-8} cycloalkyl-NH_2.

[0042] Much preferred compounds of this invention are those of the formula (I) wherein

[0043] R^1 and R^2 are methyl; R^3 and R^4 are hydrogen; and

[0044] R^5 is azabicyclo[2.2.2]octyl-piperazinyl, azabicylo[3.2.1]octanylaminoazetidinyl, diazabicyclo[3.2.1]octyl-oxomethylamino, diazabicyclo [3.2.1]octyl-oxoethylamino, methylazabicyclo [3.2.1]octyl-aminooxomethylamino, methylazabicyclo[3.2.1]octyl-aminooxoethylamino, ethylazabicyclo[3.2.1]octyl-aminooxomethylamino, piperidinopiperidinyl, [[(aminocyclohexyl)carbonyl] amino]propylamino or [[(aminocyclohexyl)carbonyl]amino]butylamino.

[0045] Also, preferred compounds of this invention are those of the formula (I) wherein

[0046] R^5 is azabicyclo[2.2.2]octyl-piperazinyl, azabicylo[3.2.1]octanylaminoazetidinyl, diazabicyclo[3.2.1]octyl-oxomethylamino, methylazabicyclo [3.2.1]octyl-aminooxomethylamino, piperidinopiperidinyl or [[(aminocyclohexyl)carbonyl]amino] propylamino.

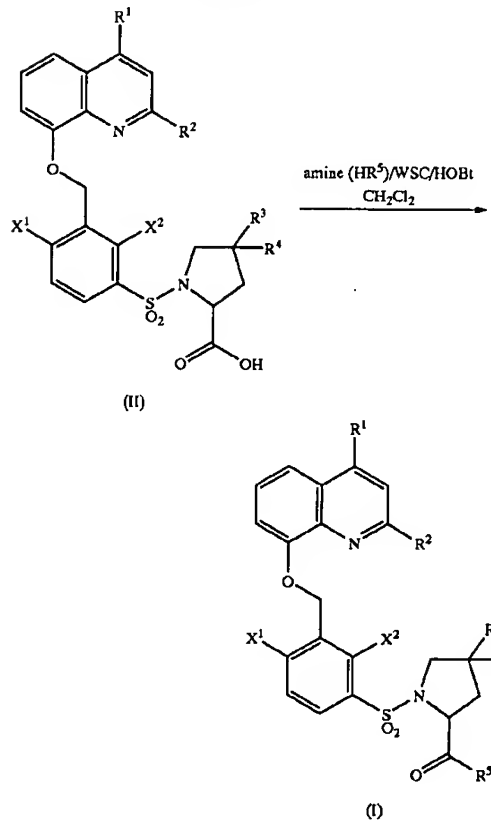
[0047] Preferred individual compounds of this invention are:

[0048] 8-[[3-[[(2S)-2-[[4-[(3S)-1-Azabicyclo[2.2.2] oct-3-yl]-1-piperazinyl]carbonyl]pyrrolidinyl]sulfonyl]-2,6-dichlorobenzyl]oxy]-2,4-dimethylquinoline; and (2S)-N-[2-(3,8-Diazabicyclo[3.2.1]oct-3-yl)-2-oxoethyl]-1-[[2,4-dichloro-3-[[(2,4-dimethyl-8-quinolinyl)oxy]methyl]phenyl]sulfonyl]-2-pyrrolidinecarboxamide, and a salt thereof.

General Synthesis

[0049] The N-benzenesulfonyl L-proline compounds of formula (I) of this invention may be prepared by a variety of synthetic methods.

Preparation Method A:



[0050] (wherein X^1, X^2, R^1, R^2, R^3, R^4 and R^5 are as already defined; and WSC is 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride, HOBt is 1-hydroxybenzotriazole hydrate.

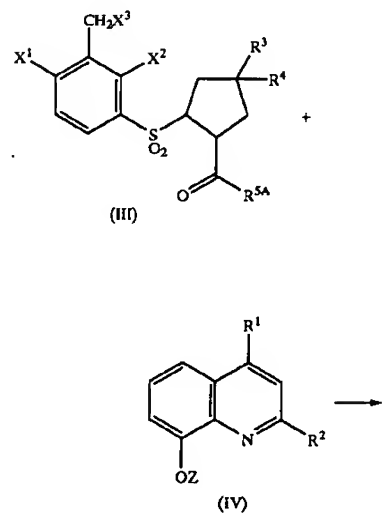
Scheme A-1

[0051] To a stirred solution of the acid of formula (II) (150 mg, 0.294 mmol) and amine H-R^5 (0.441 mmol) in CH_2Cl_2 (15 mL) were added HOBt (67 mg, 0.441 mmol) and WSC (84 mg, 0.441 mmol) at room temperature and the mixture was stirred overnight. To the mixture was added H_2O (5 mL) and the organic layer was separated, washed with saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, filtered and concentrated in vacuo. Column chromatography (NH gel, 200-350 mesh, 8 g, CH_2Cl_2/MeOH=99/1 to 90/10) afforded the coupling product including a compound of formula (I).

[0052] In the described method A, 1,3-diisopropylcarbodiimide in place of WSC, t-BuOH—CH_2Cl_2(1-1), DMF, or AcOEt in place of CH_2Cl_2 were also used. For purification process, appropriate regins or solid-phase extraction method was also utilized when the small amount of the starting material (II) (about 50 Smol) were used.

[0053] To a stirred solution of the coupling product including a compound of formula (I) (0.0964 mmol) in MeOH was added HCl-MeOH (2.9 mL) and the mixture was stirred for 15 minutes. Then the solvent was removed in vacuo to provide the HCl salt.

[0054] Alternately, the N-benzenesulfonyl L-proline compounds of formula (Ia-II) were prepared by reaction of a compound (III) with a compound of formula (IV) as indicated in the following Scheme A-II.



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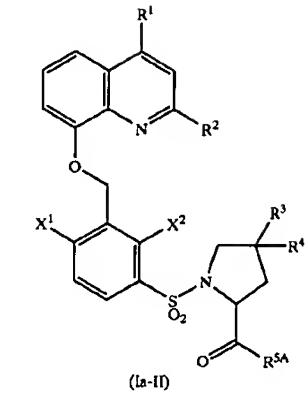


(Ia-II)

[0055] (wherein R is hydroxy, C_{1-4} alkoxy (such as methoxy and ethoxy) or R^5; X^3 is halo; and the other symbols are as already defined are as already defined)

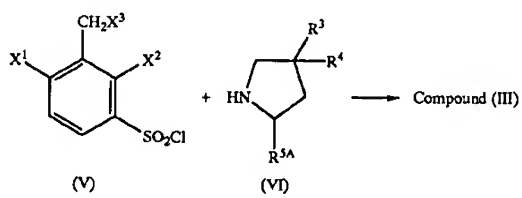
Scheme A-II

[0056] This method utilizes a synthesis as described in WO97/07115. This reaction is carried out in a suitable reaction-inert solvent (anhydrous). Suitable solvents include, for example, aromatic hydrocarbons such as benzene, toluene and xylene; alcohols such as methanol, ethanol, propanol and butanol; ethers such as diethyl ether, dioxane and tetrahydrofuran; halogenated hydrocarbons such as methylene dichloride, chloroform, dichloromethane and dichloroethane; amides such as N,N-dimethylformamide; and nitrites such as acetonitrile. This reaction is carried out at a temperature between −10° C. and 100° C., preferably from 0° C. to 50° C. for 5 minutes to 24 hours, preferably 30 minutes to 5 hours.

[0057] In addition, the compounds (III) and (IV) which can be used herein may be either already known or may be prepared according to the reported methods.

Preparation Method B

[0058] The compounds of formula (III) was prepared by the reaction of a compound (V) with a compound of formula (VI) as indicated in the following Scheme B.



(V) (VI)

[0059] (wherein X^3 is halo; and the other symbols are as already defined)

Scheme B

[0060] This method utilizes a synthesis as described in WO97/07115. This reaction is carried out in the presence of base in a suitable reaction-inert solvent. Suitable base includes, for example, triethylamine. Suitable solvents include, for example, aromatic hydrocarbons such as benzene, toluene and xylene; alcohols such as methanol, ethanol, propanol and butanol; ethers such as diethyl ether, dioxane and tetrahydrofuran; halogenated hydrocarbons such as chloroform, dichloromethane and dichloroethane; amides such as N,N-dimethylformamide; and nitrites such as acetonitrile. This reaction is carried out at a temperature between −10° C. and 100° C., preferably from 0° C. to 40° C. for 5 minutes to 24 hours, preferably 30 minutes to 3 hours.

[0061] The compounds of formula (I), and the intermediates above-mentioned preparation methods can be isolated and purified by conventional procedures such as recrystallization or chromatographic purification.

[0062] The optically active compounds of this invention can be prepared by several methods known to a skilled person in the art. For example, the optically active compounds of this invention may be obtained by chromatographic separation or fractional crystallization from the final compounds or the intermediates in racemic form thereof. Alternatively, the optically active compounds may be prepared by optically selective reaction, enzymatic hydrolysis or reactions using optically active intermediates.

[0063] The N-benzenesulfonyl L-proline compounds of this invention possess an asymmetric center. Hence, the compounds can exist in separated (+)- and (−)-optically active forms, as well as in racemic one thereof. The present invention includes all such forms within its scope. Individual isomers can be obtained by known methods, such as optically selective reaction or chromatographic separation in the preparation of the final product or its intermediate.

[0064] The present invention includes salt forms of the compounds (I) as obtained above.

[0065] Insofar as the N-benzenesulfonyl L-proline compounds of this invention are basic compounds, they are capable of forming a wide variety of different salts with various inorganic and organic acids.

[0066] The acids which are used to prepare the pharmaceutically acceptable acid addition salts of the aforementioned N-benzenesulfonyl L-proline base compounds of this invention of formula (I) are those which form non-toxic acid addition salts, i.e., salts containing pharmaceutically acceptable anions, such as the chloride, bromide, iodide, nitrate, sulfate or bisulfate, phosphate or acid phosphate, acetate, lactate, citrate or acid citrate, tartrate or bi-tartrate, succinate, malate, fumarate, gluconate, saccharate, benzoate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and pamoate (i.e., 1.1'-methylene-bis-(2-hydroxy-3-naphthoate). The acid addition salts can be prepared by conventional procedures.

[0067] The N-benzenesulfonyl L-proline compounds of the present invention of formula (I) exhibit significant bradykinin receptor-binding activity and therefore, are of value in the treatment of a wide variety of clinical conditions in mammals, especially human. Such conditions include inflammation, cardiovascular disease, pain, common cold, allergies, asthma, pancreatitis, burns, virus infection, head injury, multiple trauma and the like.

[0068] Therefore, these compounds are readily adapted to therapeutic use as bradykinin antagonists for the control and/or treatment of any of the aforesaid clinical conditions in mammals, including humans.

[0069] Also, the compounds of formula (I) may be expected more effective therapeutic effects with being co-administered with H_1-antagonist.

[0070] Further, the present invention also encompasses a pharmaceutical composition for the treatment of inflammation, rheumatoid arthritis, cystitis, post-traumatic and post ischemic cerebral edema, liver cirrhosis, Alzheimer's disease, cardiovascular disease, pain, common cold, allergies, asthma, pancreatitis, burns, virus infection, head injury, multiple trauma, rhinitis, hepatorenal failure, diabetes, metastasis, cystitis, pancreatitis, amyotrophic lateral sclerosis, Huntington's disease, Parkinson's disease, multiple sclerosis, stroke, head trauma, post-surgical brain edema, brain edema (general), cytotoxic brain edema (such as that associated with brain tumors, stroke, head trauma, etc.), brain edema associated with metabolic diseases (renal failure, pediatric metabolic diseases, etc.), rheumatoid arthritis, osteoarthritis, migraine, neuropathic pain, pruritis, brain tumor, pseudotumor cerebri, glaucoma, hydrocephalus, spinal cord trauma, spinal cord edema, neurodegenerative diseases, respiratory diseases, diuresis, natriuresis calciuresis, COPD (chronic obstructive pulmonary disease), post-traumatic brain injury, itching, sepsis, or the like, which comprises a therapeutically effective amount of the N-benzenesulfonyl L-proline compound of formula (I) and H1-antagonist or their pharmaceutically acceptable salt together with a pharmaceutically acceptable carrier.

[0071] The compounds of the invention may advantageously be employed in combination with one or more other therapeutic ingredients selected from an antibiotic, anti-fungal, or anti-viral agent, an anti-histamine, a non-steroidal anti-inflammatory drug or disease modifying anti-rheumatic drug.

[0072] The combination with an anti-histamine (H_1 antagonist) is particularly favorured for use in the prophylaxis and treatment of asthma and rhinitis. Examples of anti-histamine are chlorpheniramine, brompheniramine, clemastine, ketotifen, azatadine, loratadine, terfenadine, cetirizine, astemizole, tazifylline, levocabastine, diphenhydramine, temelastine, etolotifen, acrivastine, azelastine, ebastine, mequitazine, KA-398, FK-613, mizolastine, MDL-103896, levocetirizine, mometasone furoate, DF-1111301, KC-11404, carebastine, ramatroban, desloratadine, noberastine, selenotifen, alinastine, E-4716, efletirizine, tritoqualine, norastemizole, ZCR-2060, WY-49051, KAA-276, VUF-K-9015, tagorizine, KC-11425, epinastine, MDL-28163 terfenadine, HSR-609, acrivastine and BMY-25368.

Method for Assessing Biological Activities

[0073] The activity of the N-benzenesulfonyl L-proline compounds of the present invention, as bradykinin antagonists, is determined by their ability to inhibit the binding of bradykinin at its receptor sites in recombinant human bradykinin B_2 receptor expressing CHO-KI cells (from Receptor Biology, Inc.) employing radioactive ligands.

[0074] The bradykinin antagonist activity of the N-benzenesulfonyl L-proline compounds is evaluated by using the standard assay procedure described in, for example, Baenziger N. L., Jong Y-J. I., Yocum S. A., Dalemar L. R., Wilhelm B., Vaurek R., Stewart J. M., Eur. *J. Cell Biol.*, 1992, 58, 71-80. This method essentially involves determining the concentration of the individual compound required to reduce the amount of radiolabelled bradykinin ligands by 50% at their receptor sites in CHO-K1 cells, thereby affording characteristic IC_{50} values for each compound tested.

[0075] More specifically, the assay is carried out as follows. First, rat, guinea pig or monkey ileum tissues are minced and suspended in 25 mM piperazine-N,N'-bis (2-ethanesulfonic acid (PIPES) buffer (pH 6.8) containing 0.1 mg/ml of soybean trypsin inhibitor. Then, the tissues are homogenized using a Polytron homogenizer at setting 7 for 30 seconds three times, and then rehomogenized with a Teflon-coated homogenizer. The homogenized suspension was centrifuged at 1,200× g for 15 minutes. The pellet was rehomogenized and then centrifuged at 1,200× g for 15 minutes. These supernatant were centrifuged at 10,000× g for 60 minutes. The tissue pellets, CHO-K1 cell membrane are suspended in 25 mM PIPES buffer (pH6.8) containing 1.25 mM dithiothreitol, 1.75 [ig/ml bacitracin, 1 mM o-phenanthroline, 18.75 gtM captopril, 1.25 mg/ml bovine serum albumin (BSA), to prepare tissue/cell suspensions. Then, 10 μl of test compound solution dissolved in phosphate buffered saline (PBS, pH 7.5) containing 2% DMSO (final) and 0.1% BSA (wlv) or 10 ml of 12.5 mM bradykinin in PBS (pH 7.5) containing 0.1% BSA (w/v) are placed in a reaction 96-well plate. 15 μl of 8.3 nM [3H]bradykinin is added to the compound solution or bradykinin solution in the 96-well plate. Finally 100 μl of the tissue or cell suspension are added to the mixture in the plate, and incubated at room temperature for 1 hour under the dark. After incubation, the resultant product in the reaction plates is filtered through 0.1% polyethylenimine presoaked LKB filermat. The filtrate is washed using a Skatron auto cell harvester. The tissue bound radioactivity is determined using a LKB betaplate counter. The IC_{50} value is determined using the equation:

$$\text{Bound}=B_{max}/(1+[I]/IC_{50})$$

[0076] wherein [I] means the concentration of the test compound.

[0077] All compounds prepared in the working examples as described below were tested by this method, and showed an IC_{50} value of 0.1 nM to 4 nM in CHO-KL cells with respect to inhibition of binding at its receptor.

[0078] The most preferred compounds prepared in the working examples as described below were tested by this method, and showed an IC_{50} value of 0.5 nM to 3.3 nM in CHO-K1 cells with respect to inhibition of binding at its receptor.

[0079] The possibility of drug-drug interaction of the N-benzenesulfonyl L-proline compounds of the present invention, as bradykinin antagonists, is determined by their ability to inhibit the testosterone 6□-hydroxylase activity raised by CYP3A4 which is most abundant subtype of cytochrome P-450 in human.

CYP3A4 interaction assay

[0080] This method essentially involves determining the concentration of the individual compound required to reduce the amount of 67-hydroxytestosterone by 50%.

[0081] More specifically, the assay is carried out as follows. Human liver microsomes (0.2 mg/ml) were mixed with appropriate concentrations of kinin B2 antagonist. Then, incubated with the presence of 50 uM testosterone, 1.3 mM NADP+, 0.9 mM NADH, 3.3 mM glucose-6-phosphate, 3.3 mM $MgCl_2$, and glucose-6-phosphate dehydrogenase (8 units/ml) in a total volume of 0.2 ml of 100 mM potassium phosphate buffer, pH 7.4, at 37° C. After incubation (20 minutes), 10 μl of methylalchol containing internal standard was withdrawn. The medium was filtrated by membrane filter with centrifugation at 1,800× g for 10 minutes, and the resulting filtrate was taken.

[0082] □□6□-hydroxylated metabolite of testosterone in samples was analyzed by HPLC. A sample of 20 μl was injected to the HPLC system equipped with a Polymer Cl 8 column (2.0×75 mm). The mobile phase consisted of 24% to 66% acetonitorile linear gradient including 10 mM ammonium phosphate, and with a flow rate of 0.35 ml/min.

[0083] The IC_{50} value is determined using the equation:

$$Activity=Activity_{control}/(1+[I]/IC_{50})$$

[0084] wherein [I] means the concentration of the test compound.

[0085] The most preferred compounds as memtined above of Working Examples showed IC_{50} values of more than 10 μM.

Human Liver Microsome Assay

[0086] $T_{1/2}$ value against human liver microsome was calculated by conventional procedure. More specifically, human liver microsomes (0.2 mg/ml) were mixed with 1 μM of kinin B2 antagonist and incubated with in the presence of 1.3 mM NADP+, 0.9 mM NADH, 3.3 mM glucose-6-phosphate, 3.3 mM $MgCl_2$, and glucose-6-phosphate dehydrogenase (8 units/ml) in a total volume of 1.2 ml of 100 mM potassium phosphate buffer, pH 7.4, at 37° C. At specified incubation times (0, 5, 10, 30 minutes), an aliquot of 100 μl was withdrawn from the reaction mixture and mixed with 1 ml of acetonitrile containing internal standard. Protein was precipitated by centrifugation at 1,800× g for 10 minutes, and the resulting supernatant was taken.

[0087] Bradikinin B2 antagonist in samples were analyzed by LS/MS/MS, in a Sciex API-300 mass spectrometer linked with a Hawlett-Pakkered HP1100 HPLC system. A sample of 20 μl was injected to the HPLC system equipped with a Wakosil II 5C18 HG column (2.0×150 mm). The mobile phase consisted of 80% acetonitorile including 10 mM ammonium acetate, and the elution was isocratic with a flow rate of 0.3 ml/min. Part of the eluent from the HPLC column was introduced into the atmospheric ionization source via an ion spray interface. $T_{1/2}$ value is determined using the equation:

$$T_{1/2}=0.693/k$$

[0088] wherein k is elimination rate constant of the test compound.

[0089] The compounds of the formula (I) exhibit excellent biological activity in vitro and in vivo as bradykinin antagonists. Additionally, the compound of the formula (I) was stable against metabolism in human liver microsomes assay experiments. The most preferred compounds of Working Examples showed $T_{1/2}$ values of more than 10 minutes.

[0090] The compound of this invention showed a good IC_{50} in CHO-K1 cells and a good $T_{1/2}$ value, which are essential for a practical drug.

[0091] The N-benzenesulfonyl L-proline compounds of formula (I) of this invention can be administered via either the oral, parenteral or topical routes to mammals. In general, these compounds are most desirably administered to humans in doses ranging from 0.3 mg to 750 mg per day, preferably from 10 mg to 500 mg per day, although variations will necessarily occur depending upon the weight and condition of the subject being treated, the disease state being treated and the particular route of administration chosen. However, for example, a dosage level that is in the range of from 0.06 mg to 2 mg per kg of body weight per day is most desirably employed for treatment of inflammation.

[0092] The compounds of the present invention may be administered alone or in combination with pharmaceutically acceptable carriers or diluents by either of the above routes previously indicated, and such administration can be carried out in single or multiple doses. More particularly, the novel therapeutic agents of the invention can be administered in a wide variety of different dosage forms, i.e., they may be combined with various pharmaceutically acceptable inert carriers in the form of tablets, capsules, lozenges, troches, hard candies, powders, sprays, creams, salves, suppositories, jellies, gels, pastes, lotions, ointments, aqueous suspensions, injectable solutions, elixirs, syrups, and the like. Such carriers include solid diluents or fillers, sterile aqueous media and various nontoxic organic solvents, etc. Moreover, oral-pharmaceutical compositions can be suitably sweetened and/or flavored. In general, the therapeutically-effective compounds of this invention are present in such dosage forms at concentration levels ranging 5% to 70% by weight, preferably 10% to 50% by weight.

[0093] For oral administration, tablets containing various excipients such as microcrystalline cellulose, sodium citrate, calcium carbonate, dipotassium phosphate and glycine may be employed along with various disintegrants such as starch and preferably corn, potato or tapioca starch, alginic acid and certain complex silicates, together with granulation binders like polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very useful for tabletting purposes. Solid compositions of a similar type may also be employed as fillers in gelatin capsules; preferred materials in this connection also include lactose or milk sugar as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration, the active ingredient may be combined with various sweetening or flavoring agents, coloring matter or dyes, and, if so desired, emulsifying and/or suspending agents as well, together with such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof.

[0094] For parenteral administration, solutions of a compound of the present invention in either sesame or peanut oil or in aqueous propylene glycol may be employed. The aqueous solutions should be suitably buffered (preferably pH>8) if necessary and the liquid diluent first rendered isotonic. These aqueous solutions are suitable for intravenous injection purposes. The oily solutions are suitable for intra-articular, intramuscular and subcutaneous injection

purposes. The preparation of all these solutions under sterile conditions is readily accomplished by standard pharmaceutical techniques well known to those skilled in the art. Additionally, it is also possible to administer the compounds of the present invention topically when treating inflammatory conditions of the skin and this may preferably be done by way of creams, jellies, gels, pastes, ointments and the like, in accordance with standard pharmaceutical practice.

EXAMPLES

[0095] The invention is illustrated in the following non-limiting examples in which, unless stated otherwise: all operations were carried out at room or ambient temperature, that is, in the range of 18-25° C.; evaporation of solvent was carried out using a rotary evaporator under reduced pressure with a bath temperature of up to 60° C.; reactions were monitored by thin layer chromatography (tic) and reaction times are given for illustration only; melting points (m.p.) given are uncorrected (polymorphism may result in different melting points); the structure and purity of all isolated compounds were assured by at least one of the following techniques: tic (Merck silica gel 60 F_{254} precoated TLC plates or Merck NH_2 F_{254}s precoated HPTLC plates), mass spectrometry, nuclear magnetic resonance (NMR), infrared red absorption spectra (IR) or microanalysis. Yields are given for illustrative purposes only. Flash column chromatography was carried out using Merck silica gel 60 (230-400 mesh ASTM) or Fuji Silysia Chromatorex DU3050 (Amino Type, 30-50 μm). Low-resolution mass spectral data (El) were obtained on a Automass 120 (JEOL) mass spectrometer. Low-resolution mass spectral data (ESI) were obtained on a Quattro II (Micromass) or ZMD (Micromass) mass spectrometer. NMR data was determined at 270 MHz (JEOL JNM-LA 270 spectrometer) or 300 MHz (JEOL JNM-LA300) using deuterated chloroform (99.8% D) or dimethylsulfoxide (99.9% D) as solvent unless indicated otherwise, relative to tetramethylsilane (TMS) as internal standard in parts per million (ppm); conventional abbreviations used are: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br.=broad, etc. IR spectra were measured by a Shimazu infrared spectrometer (IR-470). Optical rotations were measured using a JASCO DIP-370 Digital Polarimeter (Japan Spectroscopic CO, Ltd.).

[0096] Chemical symbols have their usual meanings; b.p. (boiling point), m.p. (melting point), 1 (liter(s)), ml (milliliter(s)), g (gram(s)), mg(milligram(s)), mol (moles), mmol (millimoles), eq. (equivalent(s)).

Example 1

[0097] 8-[[3-[[(2s)-2-[[4-r(3S)-1-AZABICYCLO[2.2.2]OCT-3-YL]-1-PIPERAZINYL]CARBONYL]PYRROLIDINYL]SULFONYL]-2,6-DICHLOROBENZYL]OXY]-2,4-DIMETHYLQUINOLINE, HCl SALT

[0098] A. 1-[(3S)-1-Azabicyclo[2.2.2]oct-3-yl]-4-benzyl-2,6-1Piperazinedione

[0099] To a solution of N-benzyliminodiacetic acid (2.23 g, 10.0 mmol) in THF (30 mL) was added 1,1'-carbonylbis-1H-imidazole (3.57 g, 22.0 mmol) at room temperature under nitrogen atmosphere. The resulting mixture was stirred at reflux temperature for 30 min (until the evolution of CO_2 gas ceased, giving a clear solution), then cooled to room temperature. To the resulting mixture was added a solution of (3S)-3-aminoquinuclidine dihydrochloride (2.00 g, 10.0 mmol) and triethylamine (3.06 mL, 22.0 mmol) in THF (10 mL) stirred at room temperature under nitrogen atmosphere for 30 min via a cannula. The combined reaction mixture was stirred under reflux for 24 h, then cooled to room temperature and quenched with H_2O (10 mL). The organic layer was extracted with EtOAc (50×2 mL) and the combined organic layers were dried over $MgSO_4$, concentrated in vacuo. The residue was purified by column chromatography (NH gel, 200-350 mesh, 150 g, EtOAc) to give a product (2.17 g, 69%) as a white solid.

[0100] ^{1}H NMR ($CDCl_3$) δ: 7.39-7.27 (m, 5 H), 4.73-4.66 (m, 1 H), 3.77-3.69 (m, 1 H), 3.60 (s, 2 H), 3.38 (s, 4 H), 3.34-3.29 (m, 1 H), 3.02-2.93 (m, 1 H), 2.90-2.75 (m, 3 H), 1.91-1.61 (m, 4 H), 1.38-1.28 (m, 1 H)

[0101] B. (3S)-3-(4-Benzyl-1-piperazinyl)-1-azabicyclo[2.2.2]octane

[0102] To a solution of 1-[(3S)-1-azabicyclo[2.2.2]oct-3-yl]-4-benzyl-2,6-piperazinedione (1.90 g, 6.00 mmol) in 1,4-dioxane (40 mL) was added $LiAlH_4$ (911 mg, 24.0 mmol) at room temperature under nitrogen atmosphere. The resulting suspension was stirred under reflux for 3.5 h, then cooled to 0° C. The mixture was diluted with Et_2O (80 mL), then treated carefully with $Na_2SO_4$10 H_2O (9.1 g) and anhydrous KF (1 g). After the resulting white suspension was stirred vigorously at room temperature for 30 min, the white precipitate was removed by filtration through a pad of celite. The filtrate was concentrated in vacuo and the residue was purified by column chromatography (NH gel, 200-350 mesh, 40 g, EtOAc) to give a product (1.39 g , 81%) as a white solid.

[0103] ^{1}H NMR ($CDCl_3$) 67 : 7.32-7.24 (m, 5 H), 3.51 (s, 2 H), 3.01-1.98 (m, 16 H), 1.83-1.59 (m, 2 H), 1.48-1.40 (m, 1 H), 1.30-1.21 (m, 1 H)

[0104] C. (3S)-3-(1-Piperazinyl)-1-azabicyclo[2.2.2]octane

[0105] A mixture of (3S)-3-(4-benzyl-1-piperazinyl)-1-azabicyclo[2.2.2]octane (1.25 g, 4.37 mmol) and 400 mg of $Pd(OH)_2$ (20 wt % on carbon) in MeOH (60 mL) was stirred at room temperature under hydrogen atmosphere (4 atm) for 6 h. The reaction mixture was filtered through a pad of celite and the filtrate was concentrated in vacuo to give a product (850 mg, quant.).

[0106] ^{1}H NMR ($CDCl_3$) δ: 3.01-2.00 (m, 16 H), 1.81-1.65 (m, 2 H), 1.50-1.36 (m, 1 H), 1.36-1.20 (m, 1 H)

[0107] D. 8-[[3-[[(2S)-2-[[4-[(3S)-1-Azabicyclo[2.2.2]oct-3-yl]-1-piperazinyl]carbonyl]pyrrolidinyl]sulfonyl]-2,6-dichlorobenzyl]oxy]-2,4-dimethylquinoline. HCl salt

[0108] This compound was prepared by a procedure similar to that described in method A and AcOEt was used for the extraction solvent. Column chromatography (NH gel, 200-350 mesh, AcOEt/MeOH=10/1-5/1) afforded a product.

[0109] Free Base

[0110] ^{1}H-NMR (CD_3OD) 67 □ 8.09 (d, J=8.6 Hz, 1H), 7.60 (d, J=8.6 Hz, 1H), 7.58 (dd, J=8.4, 1.0 Hz, 1H), 7.44 (t, J=8.2 Hz, 1H), 7.27 (dd, J=8.4, 1.0 Hz, 1H), 7.18 (d, J=1.0 Hz, 1H), 5.70-5.44 (m ,2H), 4.94 (dd, J=8.6, 3.6 Hz, 1 H), 3.65-3.30 (m, 6H), 2.94-2.60(m, 4H), 2.59 (s, 3H), 2.53 (s,

3H), 2.35-2.15 (m, 6H), 2.05-1.90 (m, 2H), 1.90-1.55 (m, 6H), 1.45-1.20 (m, 2H) HCl salt

[0111] mp 181-184° C.

[0112] IR (KBr)vmr,: 3386, 2924 1655, 1638, 1439, 1333, 1269, 1153, 1030 cm^{-1}.

[0113] MS (m/z): 686.18 (ES+, exact mass 685.23)

Example 2

[0114] N-[1-[[(2S)-1-[[2,4-DICHLORO-3-[[(2,4-DIMETHYL-8-QUINOLINYL)OXY]METHYL]PHENYL]SULFONYL]PYRROLIDINYL]CARBONYL]-3-AZETIDINYL]-EXO-8-METHYL-8-AZABICYCLO[3.2.1]OCTAN-3-AMINE

[0115] A. 1-Benzhydrvl-3-azetidinol

[0116] A mixture of benzhydrylamine (25.0 g, 136 mmol), epichlorohydrine (12.6 g, 136 mmol) in MeOH (55 mL) was stirred for 3 days at room temperature. Then the mixture was stirred under reflux for 2 days. After cooling, the solvent was evaporated in vacuo and the resulting solid was washed with acetone (30 mL). Then the solid was suspended in Et_2O (500 mL) and washed with aqueous 6N NaOH (100 mL). The organic layer was dried over $MgSO_4$ and concentrated in vacuo to afford a product (13.6 g, 42%). This compound was used for the next reaction without further purification.

[0117] ^{1}H-NMR ($CDCl_3$) 67 : 7.38-7.14 (m, 1OH), 4.46-4.37 (m, 1H), 4.34 (s, 1H), 3.53-3.47 (m, 2H), 3.13 (brs, 1H), 2.92-2.86 (m, 2H)

[0118] B. 1-Benzhydrvl-3-azetidinone

[0119] To a stirred solution of oxalyl chloride (21.6 g, 170 mmol) in CH_2Cl_2 (270 mL) was added DMSO (26.6 g, 340 mmol) at −78° C. Then to the mixture was added dropwise a solution of 1-benzhydryl-3-azetidinol (13.6 g, 56.7 mmol) in CH_2Cl_2 (68 mL). After the mixture was stirred for 30 min, to the mixture was added triethylamine (51.6g, 510 mmol) at −78° C., and the resulting mixture was warmed to room temperature and stirred for 30 min before H_2O (50 mL) was added. The organic layer was separated, washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, 230-400 mesh, 300g, Hexane/AcOEt=7/1 to 3/1) to give a product (10.0 g, 75%) as a yellow crystal.

[0120] ^{1}H-NMR ($CDCl_3$) δ: 7.49-7.45 (m, 4H), 7.32-7.17 (m, 6H), 4.58 (s, 1 H), 3.99 (s, 4H)

[0121] C. N-(1-Benzhydryl-3-azetidinyl)-exo-8-methyl-8-azabicyclo[3.2.1]octan-3-amine

[0122] To a stirred suspension of 1-benzhydryl-3-azetidinone (4.75g, 20.0 mmol) and exo-3-aminotropane (2.80g, 20.0 mmol) was added $Ti(OiPr)_4$ (8.9 mL, 30 mmol) and the mixture was stirred at room temperature for 4h. Then to the mixture was added MeOH (90.0 mL) to dissolve the resulting precipitate. The mixture was treated carefully with $NaBH_4$ (1.14 g, 30.0 mmol) and stirred for 16h at room temperature before adding saturated aqueous $NaHCO_3$ (10 mL). After the mixture was filtered through a pad of celite, the filtrate was concentrated in vacuo, The residue was purified by column chromatography (NH gel, 200-350 mesh, 120g, CH_2Cl_2/MeOH=100/0 to 10/1) to give a product (3.45 g, 48%) as a white solid.

[0123] D. tert-Butyl 1-benzhydryl-3-azetidinyl[exo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl]carbamate

[0124] To a stirred solution of N-(1-benzhydryl-3-azetidinyl)-exo-8-methyl-8-azabicyclo[3.2.1]octan-3-amine (3.45g, 9.54 mmol) in CH_2Cl_2 (19 mL) was added Boc_2O (2.08 g, 9.54 mmol) at room temperature and the mixture was stirred for 16h before adding saturated aqueous $NaHCO_3$ (10 mL). The organic layer was extracted with CH_2Cl_2 (100 mL), dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (NH gel, 200-350 mesh, 120 g, CH_2Cl_2/MeOH =100/0 to 50/1) to give a product (4.13 g, 94%) as a yellow oil.

[0125] ^{1}H-NMR ($CDCL_3$) 67 : 7.41-7.38 (m, 4H), 7.28-7.13 (m, 6H), 4.46 (s, 1H), 4.23-4.08 (m, 2H), 3.39-3.30 (m, 4H), 3.17 (brs, 2H), 2.32 (s, 3H), 2.08-1.98 (m, 4H), 1.66-1.58 (m, 2H), 1.50 (s, 9H), 1.38-1.32 (m, 2H)

[0126] E. tert-Butyl 3-azetidinyl[exo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl]carbamate

[0127] A mixture of tert-butyl 1-benzhydryl-3-azetidinyl [exo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl]carbamate (4.13 g, 8.95 mmol) and $Pd(OH)_2$-C (20 wt % on carbon, 2.0 g) in MeOH (41 mL) was stirred under hydrogen atmosphere (4 atm) at room temperature for 8h. After the mixture was filtered through a pad of celite (30% MeOH-CH_2Cl_2, 20 mL), the filtrate was concentrated in vacuo. The residue was purified by column chromatography (NH gel, 200-350 mesh, 120g, CH_2Cl_2/MeOH=100/0 to 10/1) to give a product (3.0 g, 100%) as a white solid.

[0128] F. N-[1-[[(2S)-1-[[2,4-Dichloro-3-[[(2,4-dimethyl-8-quinolinyl)oxy]methyl]phenyl]sulfonyl]pyrrolidinyl]carbonyl]-3-azetidinyl]-exo-8-methyl-8-azabicyclo[3.2.1]octan-3-amine

[0129] The coupling product (N-Boc compound) was prepared by a procedure similar to that described in method A. Then the product was dissolved in 0.3 mL of MeOH, to which was added 4 N HCl/dioxane (150 μL, 600 1mol). The mixture was agitated by swirling for 16 h at room temperature and concentrated to dryness. The deBoc compound was purified according to the procedure described in method A.

[0130] MS (m/z): 686.59 (ES+, exact mass 685.23)

Example 3

[0131] (2S)-N-[2-(3,8-DIAZABICYCLO[3.2.1]OCT-3-YL)-2-OXOETHYL]-1-[[2,4-DICHLORO-3-[[(2,4-DIMETHYL-8-QUINOLINYL)OXY]METHYL]PHENYL]SULFONYL]-2-PYRROLIDINECARBOXAMIDE

[0132] A. Diethyl meso-1-Benzyl-2,5-pyrrolidinedicarboxylate

[0133] A solution of Diethyl meso-2,5-dibromoadipate (50 g, 139 mmol) in benzene (150 mL) was heated to reflux. Then heating was discontinued and benzylamine (50 mL) was added under stirring in 1 h. At the end of the addition, the mixture was refluxed for 20h. After cooling down, the hydrobromide salt was filtered off and washed with benzene, and the benzene solution was evaporated. The residue was distilled under reduced pressure (180-190° C./0.3 mmHg) to give a product (39.9 g, 94%) as a yellow oil.

[0134] ^{1}H NMR ($CDCl_3$, 270 MHz) δ: 7.35-7.24 (m, 5H), 4.15-3.97 (m, 4H), 3.93 (s, 2H), 2.10-2,05 (m, 4H), 1.24 (t, J =7.1 Hz, 3H), 1.19 (t, J =7.3 Hz, 3H)

[0135] B. Diethyl meso-2,5-Pyrrolidinedicarboxylate A mixture of diethyl meso-1-benzyl-2,5-pyrrolidinedicarboxylate (13.1 g, 43 mmol), $Pd(OH)_2/C$ (20% wt, 6.5 g) in MeOH was hydrogenated at 4 atm for 5h. The mixture was filtered through celite. The filtrate was concentrated in vacuo to give a product (26.3 g, 94%) as a light yellow oil.

[0136] ^1H NMR ($CDCl_3$, 270 MHz) δ: 4.24-4.15 (m, 4H), 3.99-3.94 (m, 1H), 3.85-3.77 (m, 2H), 2.24-1.86 (m, 4H), 1.28 (t, J =7.1 Hz, 6H)

[0137] C . Ethyl (2S*, 5R*)-5-[(benzylamino)carbonyl]-2-Pyrrolidinedicarboxylate

[0138] A mixture of diethyl meso-2,5-pyrrolidinedicarboxylate (26.3 g, 122 mmol), benzyamine (13.1 g, 122 mmol) in xylene (80 mL) was refluxed for 18h. After cooling down, a white solid was separated. The filtrate was evaporated and the residue was distilled under reduced pressure to remove the byproducts. (byproducts 1st fraction, 55° C./0.2 mmHg, 2nd fraction, 125° C./0.2 mmHg) The crude residue (33 g) was used for the next step.

[0139] D. 3-Benzyl-3,8-diazabicyclo[3.2.1]octane-2.4-dione

[0140] The crude ethyl (2S*, 5R*)-5-[(benzylamino)carbonyl]-2-Pyrrolidinedicarboxylate (33 g) was heated at 220° C. for 5h. Then the residue was distilled under reduced pressure (175° C., 0.3 mHg) to give a yellow oil, which included a byproduct. Then a mixture of this yellow oil and the distillation residue was purified by column chromatography (SiO_2, 230-400 mesh, 30 g, Hexane/AcOEt=2/1 to AcOEt only) to give the desired pure product (2.74 g, 10%) as a yellow oil.

[0141] ^1H NMR ($CDCl_3$, 270 MHz) δ: 7.31-7.23 (m, 5H), 4.80 (s, 2H), 4.15-4.11 (m, 2H), 2.26-2.15 (m, 2H), 1.95-1.88 (m, 2H)

[0142] E. 3-Benzyl-3.8-diazabicyclo[3.2.1]octane

[0143] To a stirred suspension of $LiAlH_4$ (1.37 g, 36.1 mmol) in dry Et_2O (23 mL) was added a solution of 3-benzyl-3,8-diazabicyclo[3.2.1]octane-2,4-dione (2.74 g, 11.9 mmol) in dry Et_2O (27.5 mL) dropwise at 0" C. Then the mixture was refluxed for 46h. After cooling down, the mixture was quenched with H_2O (1.4 mL), 15% aq. NaOH (1.4 mL) and H_2O (4.1 mL) successively, filtered through celite. The filtrate was concentrated in vacuo to provide a product (2.3 g, 96%) as a yellow oil. This product was used for the next reaction without purification.

[0144] F. tert-Butyl 3-Benzyl-3,8-diazabicyclo[3.2.1]octane-8-carboxylate

[0145] To a stirred solution of 3-benzyl-3,8-diazabicyclo [3.2.1]octane (2.30 g, 11.4 mmol) in CH_2Cl_2 (23 mL) was added Boc_2O (2.48 g, 11.4 mmol), and the mixture was stirred at room temperature overnight. Then the mixture was treated with saturated aqueous $NaHCO_3$ and the organic layers were extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified with column chromatography (SiO_2, 230-400 mesh, 69 g, Hexane only to AcOEt/Hexane =1/201, then 1/10) to give a product (2.2 g, 65%) as a colorless oil.

[0146] ^1H NMR ($CDCl_3$, 270 MHz) δ: 7.31-7.23 (m, 5H), 4.20-4.10 (m, 1H), 3.47 (s, 2H), 2.60 (dd, J=11.0, 3.0 Hz, 2H), 2.35-2.20 (m, 1 H), 1.92-1.77 (m, 4H), 1.46 (s, 9H)

[0147] G. tert-Butyl 3,8-diazabicyclo[3.2.1]octane-8-carboxylate

[0148] A mixture of tert-butyl 3-benzyl-3,8-diazabicyclo [3.2.1]octane-8-carboxylate, $Pd(OH)_2$-C (1.1 g) in MeOH (22 mL) was stirred under hydrogen atmosphere (4 atm) for 10 h at room temperature. The mixture was filtered through celite and the filtrate was concentrated in vacuo to give a product (1.45 g, 94%) as a white solid. This product was used for next step without purification.

[0149] H. tert-Butyl 3-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)acetyll-3,8-diazabicyclo[3.2.1]octane-8-carboxylate

[0150] To a stirred solution of N-phthaloylglycine (725 mg, 3.53 mmol) and fert-butyl 3,8-diazabicyclo[3.2.1]octane-8-carboxylate (500 mg, 2.36 mmol) in CH_2Cl_2 (20 mL) were added HOBt (481 mg, 3.53 mmol) and WSC (677 mg, 3.53 mmol) at room temperature and the mixture was stirred overnight. To the mixture was added H_2O (5 mL) and the organic layer was separated, washed with saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, filtered and concentrated in vacuo. Flash chromatography (SiO_2, 230-400 mesh, 309, CH_2Cl_2-MeOH=98/2 to 92/8) afforded the product as a white solid (713 mg, 81%).

[0151] ^1H NMR ($CDCl_3$, 270 MHz) δ: 7.90-7.85 (m, 2H), 7.75-7.70 (m, 2H), 4.55 (d, J=14.7 Hz, 1H), 4.36 (d, J=14.7 Hz, 1H), 4.35-4.14 (m, 2H), 3.52 (s, 2H), 3.00-2.92 (m, 1H), 2.06-1.65 (m, 3H), 1.49 (s, 9H)

[0152] I. tert-Butyl 3-(aminoacetyl)-3.8-diazabicyclof3.2.1 loctane-8-carboxylate

[0153] To a stirred solution of tert-Butyl 3-[(1,3-dioxo-1, 3-dihydro-2H-isoindol-2-yl)acetyl]-3,8-diazabicyclo[3.2.1] octane-8-carboxylate (70.0 mg, 0.187 mmol) in EtOH (1.9 mL) was added hydrazine monohydrate (19.0 mg, 0.375 mmol) at room temperature and the mixture was refluxed for 1h. After cooling, the precipitates formed were filtered off. The filtrate was evaporated in vacuo and the residue was purified by preparative TLC (SiO_2, 20×20 cm, 1 mm, CH_2Cl_2/MeOH/aqueous NH_3=92/6/2) to afford a product (21.4 mg, 42%) as a white solid.

[0154] ^1H NMR ($CDCl_3$, 270 MHz) δ: 4.30-4.20 (m, 3H), 3.50 (d, J=17.0 Hz, 1H), 3.35 (d, J=17.0 Hz, 1H), 3.36-3.30 (m, 2H), 3.00-2.87 (m, 2H), 2.00-1.90 (m, 2H), 1.72-1.58 (m, 2H), 1.48 (s, 9H)

[0155] J. (2S)-N-f2-(3,8-Diazabicyclo[3.2.1]oct-3-yl)-2-oxoethyl]-1-[[2,4-dichloro-3-[[(2,4-dimethyl-8-quinolinyl)oxy]methyl]phenyl]sulfonyl]-2-pyrrolidinecarboxamide

[0156] The titled compound was prepared by a procedure similar to that described in method A.

[0157] MS (m/z): 660.37 (ES+, exact mass 659.17)

Example 4

[0158] (2S)-1-[[2,4-DICHLORO-3-[[(2,4-DIMETHYL-8-QUINOLINYL)OXY]METHYL]PHENYL]SULFONYL]-N-[EXO-2-[(8-METHYL-8-AZABICYCLO[3.2.1]OCT-3-YL)AMINO]-2-OXOETHYL]-2-PYRROLIDINECARBOXAMIDE, HCl SALT

[0159] A. Benzylexo-3-[(8-methyl-8-azabicyclo[3.2.1] oct-3-yl)amino]-2-oxoethylcarbamate

[0160] To a solution of N-Cbz-glycine (3.58 g, 17.1 mmol) and exo-3-aminotropane2) (2.00 g, 14.3 mmol) in CH_2Cl_2 (71 mL) was added WSC (3.01 g, 15.7 mmol) at room temperature. After stirred at room temperature for 18 h, the reaction mixture was diluted with water (50 mL) and stirred at room temperature for 30 minute. The water phase was separated and extracted with CH_2Cl_2 (50 mL×2). The combined organic phase was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. Flash chromatography of the residue (NH gel, 200-350 mesh, 150 g, CH_2Cl_2/MeOH =100/1 to 50/1) afforded a product (2.18 g , 46%) as a colorless oil.

[0161] ^{1}H NMR ($CDCl_3$, 270 MHz) δ: 7.41-7.29 (m, 5 H), 5.76 (brs, 1 H), 5.46 (brs, 1 H), 5.12 (s, 2 H), 4.20-4.01 (m, 1 H), 3.80 (d, J =5.5 Hz, 2 H), 3.19-3.09 (m, 2 H), 2.26 (s, 3 H), 2.09-1.96 (m, 2 H), 1.86-1.40 (m, 6 H)

[0162] B. Exo-2-amino-N-(8-methyl-8-azabicyclo[3.2.1.] oct-3-yl)ethanamide

[0163] A mixture of benzyl exo-3-[(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)amino]-3-oxopropylcarbamate (2.71 g, 8.17 mmol) and 10% Pd on carbon (8.13 mg) in MeOH (17 mL) was stirred under hydrogen atmosphere (1atm) at room temperature for 18 h. Catalyst was removed by filtration and the filtrate was concentrated in vacuo to afford a product 1.48 g as a colorless oil. This crude product was used for the next reaction without further purification.

[0164] ^{1}H NMR ($CDCl_3$, 270 MHz) 5: 4.30-4.10 (m, 1 H), 3.27 (s, 2 H), 3.30-3.10 (m, 2 H), 2.41 (s, 3 H), 2.18-2.10 (m, 2 H), 1.90-1.60 (m, 6 H)

[0165] C (2S)-1-[[2,4-Dichloro-3-[[(2,4-dimethyl-8-quinolinyl)oxy]methyl]phenyl]sulfonyl]-N-[exo-2-[(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)amino]-2-oxoethyl]-2-pyrrolidinecarboxamide, HCl salt

[0166] The title compound was prepared by a procedure similar to that described in method A-I

[0167] Free Base

[0168] ^{1}H-NMR ($CDCl_3$) 67 : 8.12 (d, J=8.7 Hz, 1H), 7.62 (d, J=8.4 Hz, IH), 7.57 (d, J=8.4 Hz, 1H), 7.43 (t, J=7.9 Hz, 1H), 7.25-7.17 (m, 2H), 7.16 (s, 1H), 7.01 (t, J =5.5 Hz, 1H), 5.65-5.54 (m ,2H), 4.43 (dd, J=6.8, 4.6 Hz, 1H), 4.10-3.92 (m, 2H), 3.83 (dd, J=5.2, 16.8 Hz, 1H), 3.67-3.57 (m, 1H), 3.49 (dd, J=7.8, 16.1 Hz, 1H), 3.05 (brs, 2H), 2.65 (brs, 6H), 2.17 (s, 3H), 2.20-2.15 (m, 2H), 2.02-1.90 (m, 4H), 1.75-1.57 (m, 4H), 1.25 (t, J=7.5 Hz, 2H)

[0169] MS (m/z): 688.18 (ES+, exact mass 687.20)

[0170] HCl salt

[0171] mp 190-192 C

Example 5

[0172] (2S)-1-[[-1-[[2,4-DICHLORO-3-[[(2,4-DIMETHYL-8-QUINOLINYL)OXY]METHYL]PHENYL] SULFONYL]PYRROLIDINYL]CARBONYL]-4-PIPERIDINOPIPERIDINE, HCl SALT

[0173] The title compound was prepared by a procedure similar to that described in method A.

[0174] Free Base

[0175] MS (m/z): 659.19 (ES+, exact mass 658.21)

[0176] ^{1}H-NMR ($CDCl_3$) δ: 8.16 (d, J=8.6 Hz, 1H), 7.61 (d, J=8.4 Hz, 1H), 7.46 (d, J=8.4 Hz, 1H), 7.40 (t, J=8.2 Hz, 1H), 7.24 (d, J=8.6, 1.0 Hz, 1H), 7.14 (s, 1H), 5.70-5.44 (m ,2H), 5.66 (s, 2H), 5.04-4.95 (m, 1 H), 4.60-4.50 (m, 1 H), 4.00-3.77 (m, 1 H), 3.54-3.25 (m, 1 H), 3.51-3.43 (m, IH), 3.15-2.90 (m, 2H), 2.68 (s, 3H), 2.65(s, 3H), 2.60-2.40 (m, 5H), 2.30-1.30 (m, 14H)

[0177] HCl salt

[0178] mp 163-167° C.

Example 6

[0179] (2S)-1-[[3-[(2,4-DIMETHYLQUINOLIN-8-YL)OXYMETHYL]-2,4-DICHLOROPHENYL]SULFONYL]-[3-[[(3-AMINOCYCLOHEXYL)CARBONYL] AMINO]PROPYL]-2-PYRROLIDINECARBOXAMIDE, HCl SALT

[0180] A. 3-[(tert-Butoxycarbonyl)amino]cyclohexanecarboxylic acid

[0181] To a suspension of 3-aminocyclohexanecarboxylic acid (0.72 g, 5.0 mmol) in dioxane-H_2O (10 mL-5 mL) were added 1N aqueous NaOH (5.0 mL, 5.0 mmol) and di-tert-butyl dicarbonate (1.2g , 5.3 mmol) at 0° C. The mixture was stirred for 1 day at room temperature, and concentrated in vacuo. The residue was diluted with H_2O, acidified with 10% aqueous citric acid, and extracted with AcOEt. The extract was dried over $MgSO_4$, and filtered. Removal of solvent gave a product (0.97g, 76%) as a white solid.

[0182] ^{1}H-NMR ($CDCl_3$) 67 : 4.55-4.40 (1H, m), 3.55-3.35 (1H, m), 2.50-2.20 (2H, m), 2.03-1.80 (3H, m), 1.44 (9H, s), 1.40-0.95 (4H, m).

[0183] B. (2S)-1-[[(3-[(2,4-Dimethylquinolin-8-yl)oxymethyl]-2,4-dichlorophenyl]sulfonyl]-N-[3-[[3-[(tert-butoxycarbonyl)amino]cyclohexylcarbonyl]amino]propyl]-2-pyrrolidinecarboxamide

[0184] To a stirred mixture of (2S)-1-[[3-[(2,4-dimethylquinolin-8-yl)oxymethyl]-2,4-dichlorophenyl]sulfonyl]-N-(3-aminopropyl)-2-pyrrolidinecarboxamide dihydrochloride1) in CH_2Cl_2 (3 mL) was added triethylamine (33 μl, 0.23 mmol) at room temperature. After stirring for 10 min, 3-[(tert-butoxycarbonyl)amino]cyclohexanecarboxylic acid (example6-A, 23 mg, 0.094 mmol), 1-hydroxybenzotriazole (13 mg, 0.094 mmol) and WSC (18 mg, 0.094 mmol) were added at room temperature. The mixture was stirred for 18h, washed with H_2O and saturated aqueous $NaHCO_3$. After removal of solvent, the residual oil was purified by column chromatography (SiO2, 230-400 mesh, 1.5g, CH_2Cl_2/MeOH =99/1 to 90/10) to provide a product (50 mg, 81%) as a colorless oil.

[0185] ^{1}H-NMR ($CDCl_3$) 67 : 8.11 (1H, d, J=8.6 Hz), 7.64 (IH, d, J=8.2 Hz), 7.55 (1H, d, J=8.6 Hz), 7.44 (1H, t, J=8.2 Hz), 7.25 (1H, d, J=8.2 Hz), 7.16 (IH, s), 6.95-6.85 (1H, m), 6.65-6.50 (1H, m), 5.66 (2H, s), 4.54-4.40 (2H, m), 3.65-3.05 (7H, m), 2.66 (3H, s), 2.65 (3H, s), 2.30-0.90 (15H, m), 1.43 (9H, s)

[0186] C. (2S)-1-[[3-[(2,4-Dimethylquinolin-8-yl)oxymethyl]-2,4-dichlorophenyl]sulfonyl]-N-[3-[[(3-aminocyclohexyl)carbonyl]amino]propyl]-2-pyrrolidinecarboxamide, HCl salt

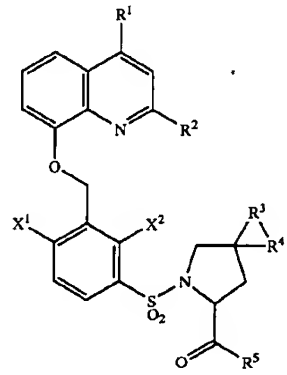
[0187] To a stirred solution of (2S)-1-[[3-[(2,4-dimethylquinolin-8-yl)oxymethyl]-2,4-dichlorophenyl]sulfonyl]-N-[3-[[3-[(tert-butoxycarbonyl)amino]cyclohexylcarbonyl]amino]propyl]-2-pyrrolidinecarboxamide (50 mg, 0.063 mmol) in MeOH (3 mL) was added HCl-MeOH (1 mL) at room temperature, and the mixture was stirred for 18h. After removal of solvent, the residual solid was triturated with AcOEt, and collected to give a product (38 mg, 79%) as a white solid.

[0188] Free Base

[0189] ^{1}H-NMR ($CDCl_3$) δ: 8.11 (1H, d, J=8.6 Hz), 7.64 (IH, d, J=8.2 Hz), 7.56 (1H, d, J=8.6 Hz), 7.44 (IH, t, J=8.2 Hz), 7.25 (1H, d, J=8.2 Hz), 7.17 (1H, s), 7.00-6.90 (1H, m), 6.70-6.55 (1H, m), 5.64 (2H, s), 4.51 (1H, dd, J=3.2,8.2 Hz), 3.65-3.05 (7H, m), 2.66 (3H, s), 2.65 (3H, s), 2.30-0.90 (15H, m)

[0190] MS (m/z): 690.22 (ES+, exact mass 689.22)

[0191] The chemical structures of the compounds prepared in the Examples 1 to 6 are summarized in the following table.



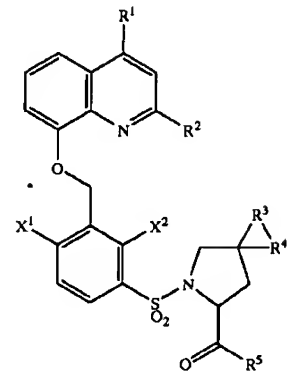
[0192] (wherein X^1 and X^2 are chloro; R^1 and R^2 are methyl; and R^3 and R_4 are hydrogen)

TABLE

Ex. #	R^5
1	4-(1-azabicyclo[2.2.2]octy-3-yl)-piperazin-1-yl
2	8-azabicylo[3.2.1]octanylaminoazetidin-1-yl
3	2-(3,8-diazabicyclo[3.2.1]oct-3-yl)-2-oxomethylamino
4	8-methyl-8-azabicyclo[3.2.1]oct-3-yl-aminooxomethylamino
5	piperidinopiperidinyl
6	[[(3-aminocyclohexyl)carbonyl]amino]propylamino

1. A compound of the formula (I):

(I)



or a pharmaceutically acceptable salt thereof wherein

X^1 and X^2 are independently halo or C_{1-4} alkyl;

R^1 and R^2 are independently hydrogen or C_{1-4} alkyl

R^3 and R^4 are independently hydrogen or halo; and

R^5 is

(a) —C_{3-9} diazacycloalkyl optionally substituted with C_{5-11} azabicycloalkyl;

(b) —C_{3-9} azacycloalkyl-NH—(C_{5-11} azabicycloalkyl optionally substituted with C_{1-4} alkyl);

(c) —NH—C_{1-3} alkyl-C(O)—C_{5-11} diazabicycloalkyl;

(d) —NH—C_{1-3} alkyl—C(O)—NH—C_{5-11} azabicycloalkyl, the C_{5-11} azabicycloalkyl being optionally substituted with C_{1-4} alkyl;

(e) —C_{3-9} azacycloalkyl optionally substituted with C_{3-9} azacycloalkyl; or

(f) —NH—C_{1-5} alkyl-NH—C(O)—C_{4-9} cycloalkyl-NH_2:

2. A compound according to claim 1, wherein

X^1 and X^2 are chloro;

R^1 and R^2 are independently hydrogen, methyl or ethyl;

R^3 and R^4 are independently hydrogen or fluoro; and

R^5 is

(a) —C_{4-8} diazacycloalkyl optionally substituted with C_{6-10} azabicycloalkyl;

(b) —C_{3-6} azacycloalkyl-NH—(C_{6-10} azabicycloalkyl optionally substituted with C_{1-4} alkyl);

(c) —NH—C, 3 alkyl-C(O)—C_{6-10} diazabicycloalkyl;

(d) —NH—C_{1-3} alkyl-C(O)—NH—C_{6-10} azabicycloalkyl, the C_{6-10} azabicycloalkyl being optionally substituted with C_{1-4} alkyl;

(e) —C_{4-8} azacycloalkyl optionally substituted with C_{4-8} azacycloalkyl; or

(f) —NH—C_{1-5} alkyl-NH—C(O)—C_5-8 cycloalkyl-NH_2.

3. A compound according to claim 2, wherein

R^1 and R^2 are methyl; R^3 and R^4 are hydrogen; and

R^5 is azabicyclo[2.2.2]octyl-piperazinyl, azabicylo[3.2.1]octanylaminoazetidinyl, diazabicyclo[3.2.1]octyl-oxomethylamino, diazabicyclo[3.2.1]octyl-oxoethylamino, methylazabicyclo[3.2.1]octyl-aminooxomethylamino, methylazabicyclo[3.2.1]octyl-aminooxoethylamino, ethylazabicyclo[3.2.1]octyl-aminooxomethylamino, piperidinopiperidinyl, [[(aminocyclohexyl)carbonyl]amino]propylamino or [[(aminocyclohexyl)carbonyl]amino]butylamino.

4. A compound according to claim 3, wherein R^5 is azabicyclo[2.2.2]octyl-piperazinyl, azabicylo[3.2.1]octanylaminoazetidinyl, diazabicyclo[3.2.1]octyl-oxomethylamino, methylazabicyclo[3.2.1]octyl-aminooxomethylamino, piperidinopiperidinyl or [[(aminocyclohexyl)carbonyl]amino]propylamino.

5. A compound according to claim 1 selected from8-[[3-[[(2S)-2-[[4-[(3S)-1-Azabicyclo[2.2.2]oct-3-yl]-1-piperazinyl]carbonyl]pyrrolidinyl]sulfonyl]-2,6-dichlorobenzyl] oxy]-2,4-dimethylquinoline; and (2S)-N-[2-(3,8-Diazabicyclo[3.2.1]oct-3-yl)-2-oxoethyl]-1-[[2,4-dichloro-3-[[(2,4-dimethyl-8-quinolinyl)oxy]methyl]phenyl] sulfonyl]-2-pyrrolidinecarboxamide, and a salt thereof.

6. A pharmaceutical composition for the treatment of disease conditions mediated by bradykinin, in a mammalian subject, which comprises a therapeutically effective amount of a compound of claim 1 or its pharmaceutically acceptable carrier.

7. A pharmaceutical composition for the treatment of inflammation, rheumatoid arthritis, cystitis, post-traumatic and post ischemic cerebral edema, liver cirrhosis, Alzheimer's disease, cardiovascular disease, pain, common cold, allergies, asthma, pancreatitis, burns, virus infection, head injury, multiple trauma, rhinitis, hepatorenal failure, diabetes, metastasis, pancreatitis, neovascularization, corneal haze, glaucoma, ocular pain or ocular hypertension, which comprises a therapeutically effective amount of a compound of claim 1 or its pharmaceutically acceptable carrier.

8. A pharmaceutical composition for the treatment of Amyotrophic lateral sclerosis, Huntington's disease, Parkinson's disease, multiple sclerosis, stroke, head trauma, post-surgical brain edema, brain edema (general), cytotoxic brain edema, brain edema associated with metabolic diseases, rheumatoid arthritis, osteoarthritis, migraine, neuropathic pain, pruritis, brain tumor, pseudotumor cerebri, glaucoma, hydrocephalus, spinal cord trauma, spinal cord edema, neurodegenerative diseases, respiratory diseases, diuresis, natriuresis calciuresis, chronic obstructive pulmonary disease, post-traumatic brain injury, itching or sepsis, which comprises a therapeutically effective amount of a compound of claim 1 or its pharmaceutically acceptable carrier.

9. A method for the treatment of disease conditions mediated by bradykinin, in a mammalian subject, which comprises administering to said subject a therapeutically effective amount of a compound according to claim 1.

10. A method for the treatment of inflammation, rheumatoid arthritis, cystitis, post-traumatic and post ischemic cerebral edema, liver cirrhosis, Alzheimer's disease, cardiovascular disease, pain, common cold, allergies, asthma, pancreatitis, burns, virus infection, head injury, multiple trauma, rhinitis, hepatorenal failure, diabetes, metastasis, pancreatitis, neovascularization, corneal haze, glaucoma, ocular pain or ocular hypertension, in a mammalian subject, which comprises administering to said subject a therapeutically effective amount of a compound according to claim 1.

* * * * *

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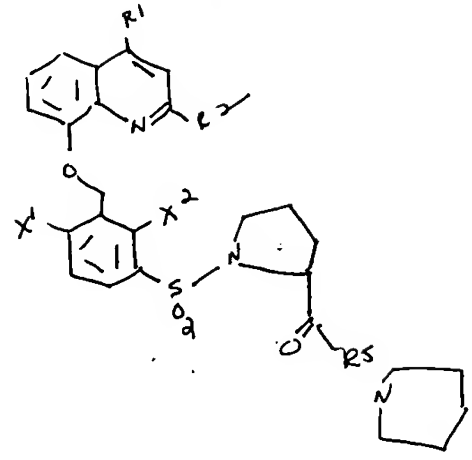

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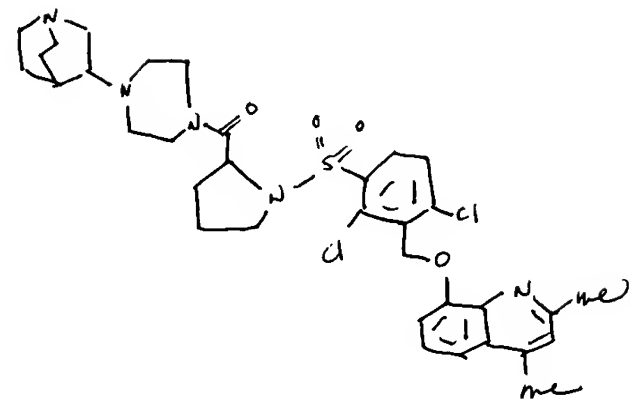

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